United States Court of Appeals
for the Federal Circuit

No. 2006-1350

BIOMEDINO, LLC,
Plaintiff-Appellant,

v.

WATERS TECHNOLOGIES CORPORATION,
Defendant-Appellee,

and

GENERAL ELECTRIC COMPANY
(doing business as GE Healthcare),
Defendant-Appellee,

and

AGILENT TECHNOLOGIES, INCORPORATED,
Defendant-Appellee.

Alisa Anne Lipski, Goldstein, Faucett & Prebeg, LLP, of Houston, Texas, argued for plaintiff-appellant. On the brief was Edward W. Goldstein.

Robert P. Taylor, Howrey LLP, of East Palo Alto, California, argued for defendant-appellee, General Electric Company (d/b/a GE Healthcare), and all other defendants-appellees. With him on the brief for General Electric Company were Matthew M. Wolf, Howrey LLP, of Washington DC, Wallace Wu, of Los Angeles, California, and Richard L.

Stanley, of Houston, Texas. With him on the brief for Waters Technologies Corporation were Aslan Baghdadi, Lawrence J. Gotts, and June E. Cohan, Paul, Hastings, Janofsky & Walker LLP, of Washington, DC. With him on the brief for Agilent Technologies, Incorporated, were James W. Geriak, Kurt T. Mulville, and Hardip B. Passananti, Orrick, Herrington & Sutcliffe LLP, of Irvine, California. Of counsel was Joseph K. Liu.

Appealed from: United States District Court for the Western District of Washington

Chief Judge Robert S. Lasnik

United States Court of Appeals
for the Federal Circuit

No. 2006-1350

BIOMEDINO, LLC,
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AGILENT TECHNOLOGIES, INCORPORATED,
Defendant-Appellee.

DECIDED: June 18, 2007

Before RADER, Circuit Judge, ARCHER, Senior Circuit Judge, and GAJARSA, Circuit Judge.

ARCHER, Senior Circuit Judge.

Biomedino, LLC ("Biomedino") appeals the

judgment of the United States District Court for the Western District of Washington that claims 13-17 and 40 of U.S. Pat. No. 6,602,502 ("the '502 patent") are invalid for indefiniteness under 35 U.S.C. § 112, ¶ 2. Biomedino v. Waters Techs. Corp., No. CV05-0042 (W.D. Wash. Mar. 15, 2006). Because the claim limitation "control means" has no corresponding structure described in the specification as required by 35 U.S.C. 112, ¶ 6, we affirm the district court's invalidity determination.

I

Section 112, ¶ 6 of Title 35 of the United States Code permits an applicant to express a claim limitation as a means or step for performing a specified function without claiming the structure that performs the function:

> An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

35 U.S.C § 112, ¶ 6 (2000).

In Valmont Industries, Inc. v. Reinke Manufacturing Co., we explained that § 112, ¶ 6 permitted "broad means-plus-function language, but provided a standard to make the broad claim language more definite[:] . . . [t]he applicant must describe in the patent specification some structure which performs the specified function." 983 F.2d

1039, 1543 (Fed. Cir. 1993). Thus, in return for generic claiming ability, the applicant must indicate in the specification what structure constitutes the means.[1] "If the specification is not clear as to the structure that the patentee intends to correspond to the claimed function, then the patentee has not paid the price but is rather attempting to claim in functional terms unbounded by any reference to structure in the specification." Med. Instrumentation & Diagnostics Corp. v. Elekta AB, 344 F.3d 1205, 1211 (Fed. Cir. 2003). Thus, "[i]f an applicant fails to set forth an adequate disclosure, the applicant has in effect failed to particularly point out and distinctly claim the invention as required by the second paragraph of § 112." In re Donaldson Co., 16 F.3d 1189, 1195 (Fed. Cir. 1994) (en banc).

The independent claims at issue in the present case recite as follows:

> 13. A device comprising a passage; binding means in said device for binding a species substantially specifically, said binding means being in fluid communication with said passage; exposure means in said device for exposing said species to said binding means and for preventing said binding means from leaving said device; closed regeneration means for separating said

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[1] Permitting an applicant to use a broad means expression for claiming a functional limitation provided that the specification indicates what structure constitutes the means for performing the claimed function is often referred to as the "quid pro quo" for the convenience of employing § 112, ¶ 6. Atmel Corp. v. Info. Storage Devices, Inc., 198 F.3d 1374, 1378 (Fed. Cir. 1999)

> species from said binding means for reuse of said binding means in said device; valving for selectively connecting said closed regeneration means in fluid communication with said binding means, and control means for automatically operating said valving.
>
> 40. A closed regeneration device for separating a molecule bound substantially specifically to a binding species for reuse of said binding species said regeneration device comprising a first reagent, a first valve selectively connecting said first reagent in fluid communication with said molecule bound to the binding species to separate said molecule from said binding species, a second reagent, a second valve selectively connecting said second reagent in fluid communication with said binding species to return said binding species to a regenerated condition, and control means for automatically operating valves.

'502 patent col.13 ll.25-35, col.16 ll.20-31 (claim terms at issue emphasized).[2] Claims 14-17 are dependent from claim 13.

The district court began its construction of the term "control means" with the observation that if a

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[2] The parties treat "control means for automatically operating said valving" and "control means for automatically operating said valves" as identical.

claim element contains the term "means" and recites a function, there is a presumption that § 112, ¶ 6 applies. Biomedino, slip op. at 8. Concluding that the inclusion of the word "control" did not identify structure and thus did not overcome the presumption that the claim limitation was a means-plus-function limitation, the district court began a § 112, ¶ 6 analysis.

The only references in the specification to the "control means" are a box labeled "Control" in Figure 6 and a statement that the regeneration process of the invention "may be controlled automatically by known differential pressure, valving and control equipment." '502 patent col.11 ll.55-58. From this, the district court concluded:

> The specification says nothing more than that unspecified equipment may be used to control the regeneration process. The fact that one skilled in the art could envision various types of equipment capable of automatically operating valves does not change the fact that no structure capable of performing that function was disclosed by the inventor.

Biomedino, slip op. at 11. As a result, the court held that "[t]he failure to disclose a structure corresponding to the 'control means' function makes claims 13-17 and claim 40 of indefinite scope in violation of § 112, ¶ 2 of the Patent Act." Id.

Biomedino appeals, and we have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

II

"A determination that a patent claim is invalid for failure to meet the definiteness requirement of 35 U.S.C § 112, paragraph 2, is 'a legal conclusion that is drawn from the court's performance of its duty as the construer of patent claims[, and i]ndefiniteness, therefore, like claim construction, is a question of law that we review de novo.'" Intellectual Prop. Dev., Inc. v. UA-Columbia Cablevision of Westchester, Inc., 336 F.3d 1308, 1318 (Fed. Cir. 2003) (quoting Atmel, 198 F.3d at 1378).

III

As an initial matter, we address Biomedino's assertion that use of the term "control" to describe "means" takes the phrase "control means" outside the realm in which § 112, ¶ 6 applies. This argument is based on the premise that "control means" recites sufficient structure on its own such that it obviates the need for § 112, ¶ 6. Biomedino argues that a "control" is a precise structure well understood by those of skill in the art, and thus, the word "means" in claims 13 and 40 can be ignored. Additionally, Biomedino contends that "control" is analogous to the term "controller" and conveys, to one skilled in the art, structure for controlling the valves and other equipment. We disagree.

When a claim uses the term "means" to describe a limitation, a presumption inheres that the inventor used the term to invoke § 112, ¶ 6. Altiris, Inc. v. Symantec Corp., 318 F.3d 1367, 1375 (Fed. Cir. 2003). "This presumption can be rebutted when the claim, in addition to the functional language, recites structure sufficient to perform the claimed function in its entirety." Id. Claims 13 and 40 recite no such structure. As the district court noted, the

"reference to 'control' is simply an adjective describing 'means:' [sic] it is not a structure or material capable of performing the identified function." Biomedino, slip op. at 12. We agree with the district court and hold that Biomedino has not rebutted the presumption that § 112, ¶ 6 applies to "control means."

B

Once a court concludes that a claim limitation is a means-plus-function limitation, two steps of claim construction remain: 1) the court must first identify the function of the limitation; and 2) the court must then look to the specification and identify the corresponding structure for that function. Med. Instrumentation, 344 F.3d 1205 at 1210. If there is no structure in the specification corresponding to the means-plus-function limitation in the claims, the claim will be found invalid as indefinite. See Atmel, 198 F.3d at 1378-79 (citing In re Donaldson, 16 F.3d at 1195).

While the specification must contain structure linked to claimed means, this is not a high bar: "[a]ll one needs to do in order to obtain the benefit of [§ 112, ¶ 6] is to recite some structure corresponding to the means in the specification, as the statute states, so that one can readily ascertain what the claim means and comply with the particularity requirement of [§ 112,] ¶ 2." Atmel, 198 F.3d at 1382. Additionally, interpretation of what is disclosed in the specification must be made in light of the knowledge of one skilled in the art. Id. at 1380. Thus, in order for a means-plus-function claim to be valid under § 112, the corresponding structure of the limitation "must be disclosed in the written description in such a manner that one skilled in the

art will know and understand what structure corresponds to the means limitation. Otherwise, one does not know what the claim means." Id. at 1382. However, "the testimony of one of ordinary skill in the art cannot supplant the total absence of structure from the specification." Default Proof Credit Card Sys., Inc. v. Home Depot U.S.A., Inc., 412 F.3d 1291, 1302 (Fed. Cir. 2005).

In the present case, there is no dispute that the claimed function is "automatically operating said valving"/"automatically operating valves." The parties also agree that the only references in the specification to the "control means" are the box labeled "Control" in Figure 6 and a statement that the regeneration process may be "controlled automatically by known differential pressure, valving and control equipment," '502 patent col.11 ll.55-58. Biomedino argues that the excerpt from the written description demonstrates that "known differential pressure equipment can be used to operate valves, known valving equipment may be used, or known control equipment may be used." Biomedino further argues that the only remaining inquiry is whether one skilled in the art would identify the structure from that description. To demonstrate that one skilled in the art would identify structure from the description in the written description, Biomedino points to two prior art references and the appellees' (collectively "Waters") own expert's testimony. Together, this evidence suggests that there were many known ways to operate valves, including pneumatically, hydraulically, mechanically, and electrically.

In response, Waters argues that there is no specific structure identified in the specification to

correspond to the claimed function of automatically operating the valves/valving: "the reference to 'differential pressure, valving and control equipment' is not at all descriptive of specific structure by which the 'control means' will automatically operate the claimed valving." As to the prior art references and expert testimony, citing Medical Instrumentation, 344 F.3d at 1212, Waters contends that the proper inquiry for identifying the structure corresponding to the recited function is "whether one of skill in the art would understand the specification itself to disclose the structure, not simply whether that person would be capable of implementing that structure."

Essentially this case asks the following question: for purposes of § 112, ¶ 6, is sufficient corresponding structure disclosed when the specification simply recites that a claimed function can be performed by known methods or using known equipment where prior art of record and the testimony of experts suggest that known methods and equipment exist? In Medical Instrumentation, 344 F.3d 1205, we came close to answering that question in the negative. In that case the alleged infringer argued that the district court improperly included software for digital-to-digital conversion as corresponding structure for the claimed "converting means." Medical Instrumentation's expert never pointed to any disclosure of structure for digital-to-digital conversion in the specification. When asked about digital-to-digital conversion in the patents, he explained that such conversion was not disclosed or discussed in the specification presumably because it was well-known in the art and required no explanation. We observed that there was no evidence to indicate that a person skilled in the art would

actually understand from the specification that software for digital-to-digital conversion was structure that corresponded to the means for converting. Id. at 1217. "Because software [wa]s not clearly linked in the specification or prosecution history to the claimed function" of converting means, we held that the district court's identification of software as a corresponding structure for § 112, ¶ 6 purposes was erroneous Id. at 1222.

In another similar case, Atmel, we also stated that the specification must disclose some structure but found that such a disclosure had been made. The claim limitation at issue in Atmel was "high voltage generating means disposed on said semiconductor circuit for generating a high voltage from a lower voltage power supply." 198 F.3d at 1376. The portion of the written description that pertained to the structural component of the means plus function limitation was the following: "the present invention may include high-voltage generator circuit 34. Known Circuit [sic] techniques are used to implement high-voltage circuit 34. See On-Chip High Voltage Generation in NMOS Integrated Circuits Using an Improved Voltage Multiplier Technique, IEEE Journal of Solid State Circuits, Vol[.] SC-11, No. 3, June 1976." Id. at 1377. Additionally, the figures of the relevant patent depicted the high-voltage generator circuit as a "black box." Id.[3]

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[3] The first part of our analysis in Atmel involved a determination of whether the district court erred by failing to assess whether sufficient structure was disclosed in the specification to support the means-plus-function limitation based on the understanding of one skilled in the art. 198 F.3d at 1380. We answered this question in the affirmative.

We began our sufficiency of the disclosure analysis in Atmel by explaining that structure supporting a means-plus-function claim under § 112, ¶ 6 must appear in the specification. Further, we noted that "consideration of the understanding of one skilled in the art in no way relieves the patentee of adequately disclosing sufficient structure in the specification." Id. at 1380. We said that a proper indefiniteness analysis "asks first whether structure is described in the specification, and, if so, whether one skilled in the art would identify the structure from the description." Id. at 1381. Thus, we concluded that the district court acted properly in ruling that the cited article could not take the place of structure that does not appear in the specification.

As noted, however, the written description in Atmel sets forth the article's title, viz., "On-Chip High Voltage Generation in NMOS Integrated Circuits Using an Improved Voltage Multiplier Technique, IEEE Journal of Solid State Circuits." Id. at 1382. Atmel's expert had testified that the article's title alone was sufficient to indicate to one skilled in the art the precise structure of the means recited in the specification. Id. Because this testimony was unrebutted, we concluded that the court improperly granted summary judgment that the patent was invalid for indefiniteness.

There is a significant difference between the facts of Atmel and those in the present case. In Atmel it was not the fact that one skilled in the art was aware of known circuit techniques that resulted in a conclusion that sufficient structure was recited. Rather, it was the inclusion in the written description of the title of the article which itself described the structure for a "known circuit

technique." Expert testimony was used to show what the title of the article would convey to one skilled in the art—in that case it was "the precise structure of the means recited in the specification." Atmel, 198 F.3d at 1382. The expert's testimony did not create or infer the structure.

In the present case, there is nothing to suggest a structure for the claimed control means. As we have previously explained, § 112, ¶ 6 requires some disclosure of structure in the specification corresponding to the claimed means. "[W]hile it is true that the patentee need not disclose details of structures well known in the art, the specification must nonetheless disclose some structure." Default Proof, 412 F.3d at 1302; see also Atmel, 198 F.3d at 1382 ("There must be structure in the specification" and the requirements of § 112, ¶ 6 will not be met when there is "a total omission of structure."); Med. Instrumentation, 344 F.3d at 1211 ("If the specification is not clear as to the structure that the patentee intends to correspond to the claimed function, then the patentee has not paid [the price for use of the convenience of broad claiming afforded by § 112, ¶ 6] but is rather attempting to claim in functional terms unbounded by any reference to structure in the specification. Such is impermissible under the statute."); Donaldson, 16 F.3d at 1195 ("[I]f one employs means-plus-function language in a claim, one must set forth in the specification an adequate disclosure showing what is meant by that language. If an applicant fails to set forth an adequate disclosure, the applicant has in effect failed to particularly point out and distinctly claim the invention as required by the second paragraph of section 112.").

The inquiry is whether one of skill in the art would understand the specification itself to disclose a structure, not simply whether that person would be capable of implementing a structure. Med. Instrumentation, 344 F.3d at 1212 (citing Atmel, 198 F.3d at 1382). Accordingly, a bare statement that known techniques or methods can be used does not disclose structure. To conclude otherwise would vitiate the language of the statute requiring "corresponding structure, material, or acts described in the specification."

IV

For the foregoing reasons, the judgment of the district court holding claims 13-17 and 40 of the '502 patent as invalid for indefiniteness is

AFFIRMED.

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON
AT SEATTLE

BIOMEDINO, LLC,
Plaintiff,

vs.

WATERS TECHNOLOGIES CORPORATION, GENERAL ELECTRI COMPANY d/b/a GE HEALTHCARE, and AGILENT TECHNOLOGIES, INCORPORATED,.
Defendants.

Civil File No. 2:05-cv-00042-RSL

JUDGMENT UNDER RULE 54(B) OF THE FEDERAL RULES OF CIVIL PROCEDURE

Defendants have moved without opposition for entry of judgment under Fed. R. Civ. P. Rule 54(b), see "Unopposed Motion for Entry of Judgment under Rule 54(b) of the Federal Rules of Civil Procedure." This Court has determined that no just reason for delay exists and directs entry of Judgment under Rule 54(b).

Claims 13-17 and claim 40 are at issue in this case and each recites "control means for automatically operating said valving." The Court has determined that the "control means" element of claims 13-17 and claim 40 is subject to § 112, ¶ 6 of the Patent Act. A failure by the patent specification to disclose adequate structure corresponding to the

recited function means that the claim is indefinite in violation of § 112, ¶ 2 of the Patent Act.

The Court determined that the "control means" element has no "corresponding structure, material, or acts described in the specification and equivalents thereto" (35 U.S.C. § 112, ¶ 6), and that claims 13-17 and 40 are therefore invalid for indefiniteness under § 112, ¶ 2. Therefore, this Court enters judgment in favor of defendants as follows:

It is ADJUDGED and DECREED that claims 13-17 and 40 of United States Patent No. 6,602,502 are indefinite and are therefore invalid for failing to satisfy the requirements of 35 U.S.C. § 112 ¶ 2.

SO ORDERED.

Dated: March 15, 2006

/s/
ROBERT S. LASNIK

United States
District Judge

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON
AT SEATTLE

BIOMEDINO, LLC,
Plaintiff,

vs.

WATERS TECHNOLOGIES CORPORATION, GENERAL ELECTRI COMPANY d/b/a GE HEALTHCARE, and AGILENT TECHNOLOGIES, INCORPORATED,.
Defendants.

Civil File No. 2:05-cv-00042-RSL

ORDER DENYING PLAINTIFF'S MOTION FOR RECONSIDERATION

On or about November 22, 2005, the Court issued an order construing the claims of the '502 patent. Plaintiff filed a timely motion for reconsideration and has challenged the Court's finding that the term "control means" is indefinite.

Motions for reconsideration are disfavored in this district and will be granted only upon a "showing of manifest error in the prior ruling" or "new facts or legal authority which could not have been brought to [the Court's] attention earlier without reasonable diligence." Local Civil Rule 7(h)(1). Plaintiff has not met this burden. Regardless of the characterization of the Kirk-Othmer and

Kitchen references, the Court properly determined that the "control means" element is subject to the means-plus-function analysis, that no "corresponding structure, material, or acts [are] described in the specification and equivalents thereto" (35 U.S.C. § 112, ¶ 6), and that claims 13-17 and 40 are therefore invalid for indefiniteness. Plaintiff's motion for reconsideration is DENIED.

DATED this 10th day of January, 2006.

/s/
ROBERT S. LASNIK

United States
District Judge

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON
AT SEATTLE

BIOMEDINO, LLC,
Plaintiff,

vs.

WATERS TECHNOLOGIES CORPORATION, GENERAL ELECTRI COMPANY d/b/a GE HEALTHCARE, and AGILENT TECHNOLOGIES, INCORPORATED,.
Defendants.

Civil File No. 2:05-cv-00042-RSL

ORDER CONSTRUING CLAIMS OF THE '502 PATENT

Plaintiff Biomedino, LLC, is the owner of United States Patent No. 6,602,502 ("the patent" or "the '502 patent"), which relates to "improved immunoassays of psychotomimetic drugs, tetrahydrocannabinols and other psychoactive drugs." Col. 1, ll. 15-17. Plaintiff's invention utilizes the haptenic properties of psychoactive material (properties which had not previously been recognized or exploited) to develop improved methods of identification, diagnosis, and treatment. Col. 2, ll. 10-41. The claims at issue in this litigation were added to the original patent application over a number of years and are written more broadly than the original claims insofar as they describe an invention capable of removing from an unspecified

fluid an unspecified constituent in the fluid. The Patent and Trademark Office ("PTO") initially rejected the new claims at least in part on the ground that the written description of the invention, which focused on its use in removing psychoactive drugs from the blood of living mammals, was of more narrow scope than the new claims. After arguing that one skilled in the art would recognize in the admittedly narrow specification a description of the more general invention now claimed, plaintiff was awarded the '502 patent. Plaintiff alleges that defendants have infringed the '502 patent by making, using, and selling products that utilize separation, affinity, and chromatography systems which embody at least one claim of the patent.

Determining whether a particular product or method infringes an existing patent involves a two-step analysis. The Court must first identify the proper construction of the asserted patent claim, an exercise which the Supreme Court has determined is a matter of law. Markman v. Westview Instruments, Inc., 517 U.S. 370, 384-91 (1996). After the claim has been properly construed, the fact finder determines whether the accused device infringes the claim. The Federal Circuit recently reiterated that, although the claims of the patent define the invention to which the patentee is entitled the right to exclude, the claim construction analysis must focus on how a person of ordinary skill in the art would understand the claim terms after reading the entire patent. Phillips v. AWH Corp., 415 F.3d 1303, 1321, 1323 (Fed. Cir. 2005).

> It is the person of ordinary skill in the field of the invention through whose eyes the claims are construed. Such person is deemed to read the words used in the patent documents with an understanding of their meaning in the field, and to have knowledge of any special meaning and usage in the field. The inventor's words that are used to describe the invention -- the inventor's lexicography -- must be understood and interpreted by the court as they would be understood and interpreted by a person in that field of technology. Thus the court starts the decisionmaking process by reviewing the same resources as would that person, *viz.*, the patent specification and the prosecution history.

Phillips, 415 F.3d at 1313 (quoting Multiform Desiccants, Inc. v. Medzam, Ltd., 133 F.3d 1473, 1477 (Fed. Cir. 1998)).

As all parties in this litigation recognize, the Phillips decision sets out a framework for claim construction that synthesizes prior law while rejecting the Texas Digital Sys., Inc. v. Telegenix, Inc., 308 F.3d 1193 (Fed. Cir. 2002), line of cases because they put too much emphasis on extrinsic evidence. The Federal Circuit highlighted the primacy of intrinsic evidence, rather than dictionaries, encyclopedias, and treatises, in the claim construction analysis. The claims themselves provide "substantial guidance" regarding the

meaning of particular terms by providing a context for the contested terms and comparisons against which to measure the scope of the various claims. Phillips, 415 F.3d at 1314-15. Unless the meaning of the claim language is "readily apparent even to lay judges" (Phillips, 415 F.3d at 1314), the court should "rely heavily" on the patentee's written description of the invention (Phillips, 415 F.3d at 1317), giving the claims "their broadest reasonable construction 'in light of the specification as it would be interpreted by one of ordinary skill in the art'" (Phillips, 415 F.3d at 1316 (quoting In re Am. Acad. of Sci. Tech. Ctr., 367 F.3d 1359, 1364 (Fed. Cir. 2004))). Other evidence of how the patentee and the PTO understood the claims contained in the prosecution history can also inform the meaning of the claim language, although this resource sometimes lacks the clarity of the patent itself. Phillips, 415 F.3d at 1317.

Finally, the Federal Circuit has "authorized district courts to rely on extrinsic evidence, which 'consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." Phillips, 415 F.3d at 1317 (quoting Markman v. Westview Instruments, Inc., 52 F.3d 967, 980 (Fed. Cir. 1995)). Such evidence is especially useful for helping the court understand the underlying technology, explaining how an invention works, and establishing the way in which one skilled in the art would use the claim terms. Phillips, 415 F.3d at 1318. Courts should not, however, put too much emphasis on extrinsic evidence as the starting point for construing claim terms because such evidence "is

unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." Phillips, 415 F.3d at 1319. The claim construction methodology set forth in Texas Digital, which encouraged district courts to rely on dictionary definitions when ascertaining the ordinary meaning of particular claim terms, with recourse to the specification serving only as a check on the dictionary definition, was rejected.

> The main problem with elevating the dictionary to such prominence is that it focuses the inquiry on the abstract meaning of words rather than on the meaning of claim terms within the context of the patent. Properly viewed, the "ordinary meaning" of a claim term is its meaning to the ordinary artisan after reading the entire patent. Yet heavy reliance on the dictionary divorced from the intrinsic evidence risks transforming the meaning of the claim term to the artisan into the meaning of the term in the abstract, out of its particular context, which is the specification.

Phillips, 415 F.3d at 1321.

Even while rejecting the methodology of Texas Digital, the Federal Circuit acknowledged that the purpose underlying that decision, namely to avoid "one of the cardinal sins of patent law -- reading a limitation from the written description into the claims," was sound. Phillips, 415 F.3d at 1319-20,

1323 (quoting SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337, 1340 (Fed. Cir. 2001)). The court also recognized:

> that the distinction between using the specification to interpret the meaning of a claim and importing limitations from the specification into the claim can be a difficult one to apply in practice. However, the line between construing terms and importing limitations can be discerned with reasonable certainty and predictability if the court's focus remains on understanding how a person of ordinary skill in the art would understand the claim terms. For instance, although the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments. In particular, we have expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment. That is not just because section 112 of the Patent Act requires that the claims themselves set forth the limits of the patent grant, but also because persons of ordinary skill in the art rarely would confine their definitions of terms to the exact representations depicted in the embodiments.

Phillips, 415 F.3d at 1323 (citations omitted).

In this litigation, plaintiff alleges that defendants have infringed claims 13-17 and claim 40 of the '502 patent. Independent claim reads as follows:

> 13. A device comprising a passage; binding means in said device for binding a species substantially specifically, said binding means being in fluid communication with said passage; exposure means in said device for exposing said species to said binding means and for preventing said binding means from leaving said device; closed regeneration means for separating said species from said binding means for reuse of said binding means in said device; valving for selectively connecting said closed regeneration means in fluid communication with said binding means, and control means for automatically operating said valving.

Claims 14-17 add various elements or limitations to the invention described in claim 13. Claim 40 independently claims the closed regeneration device, stating:

> 40. A closed regeneration device for separating a molecule bound substantially specifically to a binding species for reuse of said binding species, said regeneration device comprising a

> first reagent, a first valve selectively connecting said first reagent in fluid communication with said molecule bound to the binding species to separate said molecule from said binding species, a second reagent, a second valve selectively connecting said second reagent in fluid communication with said binding species to return said binding species to a regenerated condition, and control means for automatically operating said valves.

Having reviewed the memoranda, declarations, and exhibits submitted by the parties (including the Joint Claim Chart submitted on September 9, 2005) and having heard the arguments of counsel and the additional evidence offered at the hearing on November 17, 2005, the Court finds as follows:

(1) The term "binding means" is a means-plus-function element of claims 13-17, meaning that the patentee used functional language in the claim without reciting the specific structure that performs the function. Section 112, paragraph 6 of the Patent Act governs the interpretation of means-plus-function elements and the Court must review the specification "as a whole to determine the structure capable of performing the claimed function."[1] Budde

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[1] "An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding

v. Harley-Davidson, Inc., 250 F.3d 1369, 1379 (Fed. Cir. 2001)). "A structure disclosed in the specification qualifies as 'corresponding' structure only if the specification or prosecution history clearly links or associates that structure to the function recited in the claim." Default Proof Credit Card Sys., Inc. v. Home Depot USA, Inc., 412 F.3d 1291, 1298 (Fed. Cir. 2005) (quoting B. Braun Med. v. Abbott Labs, 124 F.3d 1419, 1424 (Fed. Cir. 1997)).

The function performed by the binding means of claims 13-17 is to bind a species substantially specifically. The specification identifies the structures corresponding to this function in a number of places, the broadest statement of which is at Col. 12, ll. 1-4. The Court finds that the species used for binding purposes (*i.e.*, the "binding means") "is a hapten, antigen including a hapten conjugated to a carrier[] or antibody . . ." and the equivalents thereof.

(2) The term "exposure means" is also a mean-plus-function element of claims 13- 17. The Court must review the specification to determine whether the patentee adequately disclosed a corresponding structure that performs the identified functions, namely to expose a species to the binding means and to prevent the binding means from leaving the device. Defendants argue that the only structure that is "clearly linked" to the exposure function of claims 13-17 is found in Figure 6 and Examples 11

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structure, material, or acts described in the specification and equivalents thereof." 35 U.S.C. § 112, ¶ 6.

and 12 (Col. 9, l. 41 - Col. 11, l. 59) wherein the patentee describes a two-chamber device with a semi-permeable membrane separating the first chamber from the second (Col. 10, ll. 23-27, 47-49). But Example 13 and the referenced Figure 7 also describe alternative structures for exposing a species to the binding means and preventing the binding means from escaping from the device. The patentee disclosed a single column with an internal matrix to which the binding means is attached. The exposure means in this example may include a synthetic polymer such as polystyrene-latex (Col. 12, ll. 4-7), a solid phase coating (Col. 12, ll. 7-9), the wall of the column (Col. 12, ll. 15-18), a honeycomb (open porosity) matrix (Col. 12, ll. 22-23), a fill of plastic beads (Col. 12, l. 23), and the equivalents thereof.

Defendants maintain that the structures identified in Example 13 and Figure 7 do not "correspond" to the exposure function described in claims 13-17 because the invention embodied in Example 13 and Figure 7 does not include all of the elements of claims 13-17, primarily the closed regeneration means. The issue is not whether Figure 7 faithfully depicts all of the elements of claim 13: rather, the Court must determine what structure is disclosed in the specification that corresponds to the exposure function. The patentee clearly associates the exposure chambers of both Figure 6 and Figure 7 with the exposure function recited in claims 13-17 and is entitled to a construction of "exposure means" which takes into consideration all of the corresponding structures recited in Examples 11-13 and Figures 6 and 7.

(3) The term "closed regeneration means" of claims 13-17 is a means-plus-function element with the function of separating a species from its binding means so that the binding means can be reused. This function, to which all parties subscribe, does not turn on whether the regeneration means is "open" or "closed." The Court therefore agrees with plaintiff that "regeneration means" should be construed using the means-plus-function analysis and that "closed" should be separately construed in keeping with its ordinary meaning to one skilled in the art.

Plaintiff has disclosed two structures in the specification that are capable of performing the regeneration function of claims 13-17: the two-chamber, semi-permeable membrane system described in Figure 6 and Example 12 (Col. 11, ll. 32-35 and 44-50) and the single-chamber device described in Figure 7 and Example 13 (Col. 11, l. 66 - Col. 12, ll. 1 and 32-35). "[P]roper application of § 112, ¶ 6 generally reads the claim element to embrace distinct and alternative described structures for performing the claimed function." Creo Prods., Inc. v. Presstek, Inc., 305 F.3d 1337, 1346 (Fed. Cir. 2002). Both of the devices disclosed in Figures 6 and 7 can be used to strip a species from its binding means so that the binding means can be reused. Both structures are therefore included in the meaning of "regeneration means."

In the context of the patent at issue here, "closed" means within or part of the device, as opposed to outside or separate from the device.

(4) Claims 13-17 and claim 40 provide for "control means for automatically operating said valving." Plaintiff argues that the phrase "control means" itself identifies sufficient structure to satisfy § 112, ¶ 6 because one of skill in the art would understand that "control" refers to an instrument used to operate, regulate, or guide a machine or vehicle. Plaintiff's Opening Brief at 19 (Dkt. # 90). If a claim element contains the word "means" and recites a function, there is a strong presumption that the element is a means-plus-function element. Envirco Corp. v. Clestra Cleanroom, Inc., 209 F.3d 1360, 1364 (Fed. Cir. 2000). The presumption can collapse if the claim term recites no function or recites sufficient structure to perform the function. Apex Inc. v. Raritan Computer, Inc., 325 F.3d 1364, 1372 (Fed. Cir. 2003). The control means element of the claims at issue here clearly identifies a function: to automatically operate valving. To determine whether the element discloses sufficient structure to perform this function, the court examines whether the term, "as the name for the structure, has a reasonably well understood meaning in the art." Apex, 325 F.3d at 1372 (quoting Greenberg v. Ethicon Endo-Surgery, Inc., 91 F.3d 1580, 1583 (Fed. Cir. 1996)). Contrary to plaintiff's argument, claims 13-17 and claim 40 do not recite any structure for operating the valves. The reference to "control" is simply an adjective describing "means:" it is not a structure or material capable of performing the identified function. Where the presumption applies, courts have generally required a fairly detailed recitation of structure to take a "means for" claim element out of the scope of § 112, ¶ 6. See, e.g., Phillips, 415 F.3d at 1311 (claim element beginning

with "further means disposed inside the shell for increasing its load bearing capacity" is not means-plus- function format because the claim subsequently identifies "internal steel baffles" as the structure that performs the function); Rodime PLC v. Seagate Tech., Inc., 174 F.3d 1294, 1303- 04 (Fed. Cir. 1999) (construction of a claim element beginning with a "positioning means for moving said transducer . . ." was not governed by § 112, ¶ 6 where the claim specifically identified the underlying structures as including "two support arms . . . a pivot shaft . . . a positioning arm . . . a bearing assembly . . . a stepper motor . . . means for operating said stepper motor . . . and a tensioned steel band . . ."). The patentee's inclusion of the word "control" does identify structure and does not overcome the presumption that the "control means" element is subject to the means-plus-function analysis.

Having determined that the "control means" element of claims 13-17 and claim 40 is subject to § 112, ¶ 6 of the Patent Act, the Court must determine whether the patentee "set forth in the specification an adequate disclosure showing what is meant by that language." Default Proof, 412 F.3d at 1298 (quoting In re Donaldson Co., 16 F.3d 1189, 1195 (Fed. Cir. 1994)). A failure to disclose adequate structure corresponding to the recited function means that the claim is of indefinite scope in violation of § 112, ¶ 2 and is therefore invalid. Claims of a patent are afforded a statutory presumption of validity, however, which places the burden on defendants to establish by clear and convincing evidence any facts supporting a holding

of invalidity. Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co., 204 F.3d 1360, 1367 (Fed. Cir. 2000). "Thus, a challenge to a claim containing a means-plus-function limitation as lacking structural support requires a finding, by clear and convincing evidence, that the specification lacks disclosure of structure sufficient to be understood by one skilled in the art as being adequate to perform the recited function." Budde, 250 F.3d at 1376-77.

The parties agree that the only references in the specification to the "control means" are the box labeled "Control" in Figure 6 and a statement that the regeneration process may be "controlled automatically by known differential pressure, valving and control equipment." Col. 11, ll. 55-58. "Whether or not the specification adequately sets forth structure corresponding to the claimed function necessitates consideration of that disclosure from the viewpoint of one skilled in the art." Budde v. Harley-Davidson, Inc., 250 F.3d 1369, 1376 (Fed. Cir. 2001). Plaintiff argues that the "control equipment" mentioned at Col. 11, ll. 55-58 is the structure that corresponds with the "control means" element of the claims and that, given the state of the art at the time the patent issued, one skilled in the art could draw on his or her knowledge "to flesh out the '502 patent's reference to 'control.'" Plaintiff's Responsive Brief at 16. In particular, plaintiff identifies two prior art references which, taken together, show that one of ordinary skill in the art would understand that timers, actuators, switches, potentiometers, valves, capacitors, and their equivalents could be used to "control" the valves as described in claims 13-17 and claim 40.

Putting aside the fact that plaintiff failed timely to disclose the extrinsic evidence upon which its proposed construction relies, "[i]t is not proper to look to the knowledge of one skilled in the art apart from and unconnected to the disclosure of the patent." Default Proof, 412 F.3d at 1300 n.2 (quoting Med. Instrumentation & Diagnostics Corp. v. Electa AB, 344 F.3d 1205, 1211-12 (Fed. Cir. 2003)). The specification says nothing more than that unspecified equipment may be used to control the regeneration process.[2] The fact that one skilled in the art could envision various types of equipment capable of automatically operating valves does not change the fact that no structure capable of performing that function was disclosed by the inventor.[3] The issue is not whether prior art or a skilled artisan could supply a structure corresponding to the identified function: the inquiry under § 112, ¶ 2 asks first "whether structure is described in specification, and, if so, whether one skilled in the art would identify the structure from that description." Atmel Corp. v. Information Storage Devices, 198 F.2d 1374, 1381 (Fed. Cir. 1999)). See also Default Proof, 412 F.3d at 1302 ("while it is true that the patentee need not disclose

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[2] In this context, the phrase "control equipment" is no more specific or defining than the phrase "control means." Neither phrase identifies the structures, materials, or mechanisms used to operate the valves described in claims 13-17 and claim 40

[3] Plaintiff has not offered expert testimony in support of its arguments regarding what one skilled in the art would understand from the phrase "control means" or "control equipment."

details of structures well known in the art . . . , the specification must nonetheless disclose some structure. Stated differently, the testimony of one skilled in the art cannot supplant the total absence of structure from the specification."). Because no structure corresponding to the specified function is described, defendants have shown by clear and convincing evidence that the '502 patent fails at the first hurdle. The failure to disclose a structure corresponding to the "control means" function makes claims 13-17 and claim 40 of indefinite scope in violation of § 112, ¶ 2 of the Patent Act. The Court cannot and will not remedy the patentee's failure by reading into the specification prior art references, dictionary definitions, or counsel's observations regarding what one skilled in the art would have understood.

(5) The term "species" as used in claims 13-17 is not clearly defined in the specification. Although the inventor discusses haptens, antigens including a hapten conjugated to a carrier, and antibodies in the specification, there is no indication that the term "species" must be or should be limited to those molecules. The same term is used in claim 1 and subsequently narrowed in dependent claim 10 to include only haptens and antigens that are bound immunologically. "The presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." Phillips, 415 F.3d at 1315. In addition, the prosecution history clearly shows that the inventor was broadly claiming an invention capable of removing a constituent from a fluid, without limitation on the type of constituent.

See Decl. of Wallace Wu, Ex. B at GE 00011495 ("claimed invention relates to a method and a device for removing a constituent from fluid"), GE 00011505-08 (claiming non-immunological specific binding systems of chemical species). Rather than simply using the specification to interpret the meaning of the disputed term, defendants seek improperly to import limitations from the specification into the claim. Defendants argue that cases such as Nystrom v. Trex Co., Inc., 424 F.3d 1136 (Fed. Cir. 2005), support such an importation. In Nystrom, however, both the specification and the prosecution history showed that the patentee intended to limit the broad language used in the claims. In the case at hand, the intrinsic record does not speak clearly as to the intent of the patentee: the claim language and the prosecution history support a broad reading of the term "species" while the examples provided in the specification could be read to narrow the claim terms. In such circumstances, the limitations of the preferred embodiment should not be read into broad claims that were presented to, debated with, and finally approved by the PTO after considering the very overbreadth objections raised by defendants here. Nor does the extrinsic evidence provided by Dr. Hermodson alter the analysis. Such evidence is generally less reliable than the patent and the prosecution history (Phillips, 415 F.3d at 1318) and, in this case, Dr. Hermodson's opinion that one skilled in the art would understand the term "species" to mean only "a hapten, antibody [sic], or antibody from the blood of a living mammal" is unsupported. He offers no explanation for such a limitation other than his apparent belief that it is compelled by the specification.

Defendants' argument that "species" must be limited to constituents from the blood of a living mammal fails for similar reasons. Although the specification discloses uses of the invention with catheters connected to the artery of a living mammal, there is nothing about the term "species" which requires such a limitation. The fact that the same term is used in claim 1 and further limited in claim 9 to describe the removal of "a species from the blood of the mammal" raises a presumption that this limitation is not inherent in the term "species." The prosecution history contains the patentee's argument that the invention is not limited to devices designed to draw blood from a living mammal and is instead capable of purifying any number of fluids from any number or sources. Decl. of Wallace Wu, Ex. B at GE 00011508-10.

Although the specification describes very specific embodiments of the invention, the intrinsic evidence does not support defendants' argument that the claims should be confined to those embodiments. As noted by the Federal Circuit in Phillips, such a finding is necessary "not just because section 112 of the Patent Act requires that the claims themselves set forth the limits of the patent grant, but also because persons of ordinary skill in the art rarely would confine their definitions of terms to the exact representations depicted in the embodiments." Phillips, 415 F.3d at 1323.

(6) Defendants' proposed construction of the term "molecule" in claim 40 is equally unavailing. The term itself is not ordinarily limited to immunological constituents found in the blood of a

living mammal and the intrinsic evidence neither compels nor supports such a limitation. The limitation in dependent claim 41 to a device "wherein the binding species binds the molecule immunologically" suggests that the molecule mentioned in claim 40 is not so limited. To the extent that the term "species" as used in claims 13-17 is the equivalent of the term "molecule" as used in claim 40, the patentee's express intent to claim an invention broad enough to cover non-immunological binding systems shows that defendants' importation of a limitation from the specification is not warranted.

(7) The term "passage" as used in claims 13-17 is not limited to a blood passage traveling from a living mammal through a dialysis system and back to the living mammal. "Passage" has a much broader ordinary meaning that is consistent with the broad nature of the claimed invention and the patentee's arguments before the PTO. The examples provided in the specification should not be imported into the claim, especially where other claims expressly limit the term "passage" to a "passage means for said blood." See claim 1.

(8) The phrases "binding a species substantially specifically" in claims 13-17 and "bound substantially specifically" in claim 40 mean that the constituent in the fluid is bound with a high specificity. The phrase does not require anything other than substantial specificity: defendants' attempt to require a strong or immunologic interaction based on the examples provided in the specification is improper in light of the broad claim

language, other claims that require immunological binding (see claim 41), and the patentee's statements to the PTO regarding his intent to claim an invention broad enough to cover non-immunological binding
systems.

(9) In light of the Court's construction of "closed regeneration means," no further construction of the phrase "closed regeneration device" is necessary.

(10) In light of the Court's construction of "species" and "binding a species substantially specifically," no further construction of the phrase "binding species" is necessary.

(11) In light of the Court's construction of "species," "binding means," "binding a species substantially specifically," and "molecule," no further construction of the phrases "a first reagent . . . to release said species from said binding means" or "a first reagent . . . to separate said molecule from said binding species" is necessary.

(12) In light of the Court's construction of "exposure means," "binding means," and "species," no further construction of the phrase "means for exposing said binding means to a reagent to release said species from said binding means" is necessary.

It is so ORDERED.

DATED this 22nd day of November, 2005.

/s/
ROBERT S. LASNIK

United States
District Judge

UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WASHINGTON
AT SEATTLE

BIOMEDINO, LLC,
Plaintiff,

vs.

WATERS TECHNOLOGIES CORPORATION, GENERAL ELECTRI COMPANY d/b/a GE HEALTHCARE, and AGILENT TECHNOLOGIES, INCORPORATED,
Defendants.

Civil File No. 2:05-cv-00042-RSL

MARKMAN HEARING TRANSCRIPT
PROCEEDINGS BEFORE THE HONORABLE
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November 17, 2007

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MR. BAGHDADI:
Waters would like to call Professor Hage, [32] please.

DAVID HAGE, BEING SWORN, TESTIFIED AS FOLLOWS:

THE CLERK:
Please state your full name and spell your last name for the court reporter.

THE WITNESS:
My name is David Scott Hage, H-a-g-e.

DIRECT EXAMINATION

BY MR. BAGHDADI:

Q. Professor Hage, could you tell us what your present position is?
A. My present position is I'm a full professor of analytical and environmental chemistry in the chemistry department at the University of Nebraska Lincoln.
Q. And is your experience on the CV sheet that's attached to your expert report?
A. Mm-hmm, that's correct.

MR. BAGHDADI:
Would it be okay, Your Honor, if we accept – pretend that Professor Hage is an expert in the field of immuno – biological chemistry, liquid chromatography and immunological interactions.

THE COURT:
You have no objection, counsel?

MR. FAUCETT:
No, I don't, but I think we will have some cross-examination.

THE COURT:
Okay. Great. Thanks for letting me know. Yes, the professor is an expert and may testify in those areas. Go ahead, counsel. [33]

Q. (By Mr. Baghdadi) Professor Hage, did you prepare a report in connection with this hearing?
A. Yes, I did.

MR. BAGHDADI:
And we submitted to the Court, Your Honor, as Defendant's Exhibit 521

THE COURT:
Yes, I do have it, and I've reviewed it. Thank you.

Q. (By Mr. Baghdadi) Does that report accurately reflect your observations and opinions?
A. Yes, it does.

MR. BAGHDADI:
Your Honor, Waters request that Doctor Hage's report be moved into evidence.

THE COURT:
Well, we can make it an exhibit for the purposes of

the hearing here today. And I have reviewed it and it is part of the files in the case.

Q. (By Mr. Baghdadi) Doctor Hage, you've listened to Professor Hermosdon's testimony with respect to the meaning of closed regeneration device and closed regeneration means?
A. Yes, I did.
Q. Do you agree with Professor Hermodson?
A. I agree with his conclusions.
Q. Do your opinions differ from Professor Hermosdon's opinion in any significant respect?
A. No, no significant respect I can think of.
Q. What do the two of you agree on? [34]

A. Well, in terms of the closed regeneration means, we both agree that that applies to the items shown in Figure 6 and not to Figure 7. We both agree that the closed regeneration means includes in the case compartments 24 and 34 of the membrane, separating those. And the buffer containers through which the two agents are delivered.

He also mentions passages, I mention valves, as part of the system. In terms of closed regeneration device we have similar conclusions.
Q. What do you believe are the essential elements of the closed regeneration device?
A. Well, in this case it would be the two compartments, 24 and 34, the semipermeable membrane separating those two. The buffer containers delivering the reagents to that system. The valves allow that delivery. And then the control means for the valves.

Q. And what is your support for your conclusions?
A. That is based on, first of all, the fact that the only structure given in the patent for that closed regeneration means is the item in Figure 6. Also the prosecution history, Exhibit 517, page 15. I was actually reading from that. The top of the page, where it says, closed resignation means compartments 24 and 34, membrane 35, buffer containers 40 and 41, valves and control for separating said species from said binding means for reuse of said binding in said device.

THE COURT:
When you're reading it, since it is kind of [35] difficult for the court reporter -- you were just reading from an exhibit.

THE WITNESS:
Right.

THE COURT:
Exhibit 517. We'll get it later.

THE WITNESS:
Top of page 15.

Q. (By Mr. Baghdadi) Okay. Thank you. Let's move on to the control means for automatically operating said valves. What did you conclude is the function recited in that term?
A. The control means was for operating the valves in the system.

Q. And what does that function actually have to do?

A. Well, we would change the position of the valves to allow movement of the fluid in this system, such as the two reagents entering for closed regeneration.

Q. Of the two figures that were shown earlier today, Figure 6 and Figure 7, which one shows a -- which one would that function apply to?

A. The only one that shows valves is Figure 6.

Q. What structure is described in the patent figures or in the patent text for automatically operating the valves?

A. The only mention in the text is in column 11, again approximately line 55, where it simply says that the entire process regenerating antibody being controlled automatically by known differential pressure valving and control equipment.

And there's also in Figure 6 a box labeled control with a dash going to the valves represented by the symbol V inside of a [36] circle.

Q. What can you conclude as to the structure of the control means from that mark in Figure 6?

A. The only information is given us in terms of the control label placed in the box. There is no information given on that contained for the extent.

Q. What could possibly have been used in 1972 in order to automatically operate the valves?

A. Well, there are many ways of operating valves even at that date. There was pneumatic, hydraulic, mechanical, electrical means of actuation. In liquid chromatography, for example, both mechanical and pneumatic were commonly used at that time.

It could have involved sensors to look at fluid level changes. It could have been a pH sensor to look at changes in the pH, other agents within the buffer containers and the compartments. There are many possibilities.

Q. Is there anything in the text that tells you what that control means is?

A. Nothing other than what I just said.

Q. Were you also asked to consider the meaning of the term "substantially specific binding"?

A. Yes, I was.

Q. Does that term have a commonly accepted meaning in the art back in 1972?

A. Well, the combination substantially specific binding is [37] unusual. Specific binding, which referred to ligands, could be broken up into highly specific ligands or groups of specific ligands. The term substantially with that to me indicates a magnitude. In this case a large degree of binding, which would represent highly specific binding, strong binding, as is characteristic of the antibodies in immunological agents given in the patent.

Q. Is your conclusion supported by the prosecution history?

A. Yes. There is an Exhibit 508, a line in which the applicant states that the claims are, therefore, not as broad as examiner apparently fears are limited to the immunological binding partners disclosed and the equivalents thereof.

Q. Thank you, doctor Hage. Let's move on to the next exposure means in said device for exposing said species to said binding means and for preventing said binding means from leaving said device. Did you

form an opinion with respect to the meaning of that term?

A. Yes, I did.

Q. And what's your opinion there?

A. My opinion was that this, again, referred to the device in Figure 6, similar to Professor Hermodson. It involved the chambers in that system for exposing the fluid to the blood and also the semipermeable membrane. It's also supported by the prosecution history.

Q. Now, which column in Figure 6 are you referring to?

A. I am referring to -- the exposure means would be the chamber [38] 32, semipermeable membrane 33.

Q. Now, was that structure linked to the function of the prosecution history?

A. Yes, it was. It is indicated on Exhibit 517, page 14, near the bottom of the page.

Q. Could you read that, please, slowly.

A. It says exposure means semipermeable membrane 33 and second compartment 32 in said device for exposing said species to said binding means for preventing said binding means from leaving said device.

Q. You did speed up. Does that structure perform the recited function?

A. It performs most of the recited function. It certainly allows contact for exposure. It also prevents the antibody or binding agent from leaving the system on that side of the device. However, I feel that also chamber 34 and semipermeable membrane also are needed to keep the antibody in the system to

prevent it from being washed out during the regeneration step.

Q. So without semipermeable membrane 35, what would happen to the antibodies?

A. During the regeneration, when it's dissociated from the agents bound to, they would both be washed off to the drain at the bottom of that diagram.

MR. BAGHDADI:
Your Honor, that's all I have. Thank you. [39]

THE COURT:
Okay. Mr. Faucett, you had some questions.

MR. FAUCETT:
Yes, Your Honor, if you don't mind. Quickly.

CROSS-EXAMINATION

BY MR. FAUCETT::

Q. Would you say your name one more time, sir? I apologize.

A. David S. Hage.

Q. Hage.

A. Hage, that's correct.

Q. I've heard it pronounced a number of different times. Doctor Hage, what year did you earn your undergraduate degree?

A. I earned my Bachelor in science and chemistry and biology in 1983.

Q. Okay. So in -- how old are you know?

A. 44.

Q. You are a young looking 44. So in 1972 you were what?
A. I turned 11 in April that year.
Q. Okay. So when you were offering your opinions earlier as to what a person of ordinary skill in the art in 1972 was thinking or doing, that's not based on your own personal experience?
A. No. It's based on my analysis of scientific literature and my own view of that literature. For example, I've read reviews on the history of liquid chromatography going back not just to 1972, but actually going back to 1910.
Q. Fair enough. I just want to make clear it's not your own [40] personal knowledge, it's what you read or what other people may have told you?
A. Mm-hmm.

MR. FAUCETT:
Okay. Fair enough. Pass the witness, Your Honor. [41]

Kirk-Othmer, Encyclopedia of Chemical Technology, Second Edition, vol. 11, John Wiley & Sons Inc., 1966, pp. 887-895

Pressure Drop. The pressure drop for the required flow through an exchanger bed is related to particle size, shape, uniformity, and compressibility as well as to solution viscosity and flow rate. The pressure-drop characteristics of a spherical cation exchanger of two size ranges are shown in Figure 10.

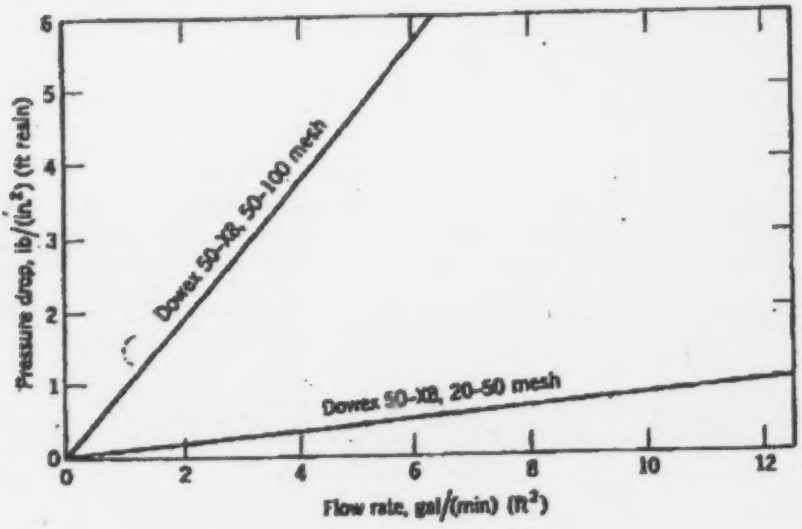

Fig. 10. Head loss characteristics at various flow rates at 25°C

Areas of Application

Water Softening. The treatment of water has always been the dominant area of ion-exchange applications; there are no signs that it will relinquish its position. In this area, water softening accounts for the major tonnage of resin sales. Hard

waters which contain principally calcium and magnesium ions cause scale in powerplant boilers, water pipes, and domestic cooking utensils. Hard waters also cause soap precipitation producing an undesirable gray curd and a waste of soap. Water softening involves the interchange of one hard ion (calcium) for another soft ion of like change (sodium) on the resin. Typically, hard water is passed through a bed of a sodium-form cation-exchange resin and softened.

$$2\ RNa^{+} + Ca^{2+} \rightarrow R^{2}Ca^{2} + 2\ Na^{+}$$

Regeneration of the exchanger involves the passage of a fairly concentrated (6-20%) solution of sodium chloride through the resin.

$$R^{2}\ Ca^{2+} + 2\ Na^{+} \rightarrow 2\ RNa^{+} + Ca^{2+}$$

Typically, a gallon of hard water contains upward of 5 grains $CaCO^{3}$ (1 gr/gal = 0:017g/Iiter). All idea of the operating capacity for a particular resin-water system may be gained by referring to Figure 6.

Water Deionization. Water softening at best provides only partial removal of solids. Industrial boilers require increasingly pure water as boiler temperatures and pressures are increased, to prevent both scaling and corrosion of boiler tubes and turbine
blades. Deionization by ion exchange provides the most common solution to the problem. Deionization of water for drinking purposes is practiced to a limited degree ill regions or high-salinity water. Deionized water is or general Use ill the laboratory;

it is used in the garage or service station for battery water; it is used in the home for steam irons.

Deionization may be conducted by a number of alternative processes depending on requirements of water quality and economics. Generally, deionization requires the successive steps of strong-acid cation and strong-base union exchange or vice versa.

$$RH^{+} + NaC1 \rightarrow RNa^{+}.+ HC1$$

$$ROH^{-} + HC1 \rightarrow RC1^{-} + H2O$$

Resin regeneration is accomplished with a mineral acid solution, HC1 or H2SO for the cation exchanger and a base, such as NaOH, for the anion exchanger.

Where complete deionization is not a requirement, a weak-acid or weak-base exchanger may he substituted. Because of the efficiency of weak-base resin regeneration it is now a common practice to remove the bulk of the acid with the weak-base resin and "polish" for silica removal with a strong-base resin in a three-bed system.

After passage through the cation exchanger silicon exists in solution as very weak si1icic acids, monomers and low-molecular-weight (lmw) polymers. These acids are too weakly dissociated to form a stable salt with the weak-base resin.

strong weak strong
→ acid → base → base
resin resin resin

Still higher-quality water is obtained with a four-bed system.

strong weak strong strong
→ acid → base → acid → base
resin resin resin resin

For water containing a high level of carbonates, the interspersion of a CO2-degasser unit of some design following the cation exchanger is often practiced to reduce the load on the resin since the CO2 in solution would he picked up by the anion exchanger as HCO3.

Mixed-bed resins containing near equivalent quantities of regenerated cation and anion resin give very high-quality water, a resistance in excess of 10^7 Ω-cm being attainable. Such water quality is required when removing radioactive contaminants as are encountered in nuclear power plants. Also in washing highly specialized electronic parts, as TV tubes, or in highly critical laboratory experiments, is such quality required. Throw-away units as used in the home or laboratory arc often mixed-bed for convenience rather than: quality.

Water – Miscellaneous. In addition to the principal processes of softening and deionization already discussed there are a great number of others which are also in commercial practice (31). Dealkalization by chloride anion exchange is a process in which such anions as sulfate, bicarbonate, and carbonate, which tend to form insoluble salts with polyvalent metal ions, are replaced with chloride ions.

$$2RC1^- + COa^{2-} \rightarrow RaCOa + 2\ Cl^-$$

Simultaneous softening and partial deionization may be accomplish by contacting a portion of the raw

water with an acid-form exchanger and the balance with the sodium form of the same exchanger. The proportion contacting the cation exchanger is something less than the carbonate-bicarbonate fraction of the raw water, thus producing CO2, which may be removed if desired, although in any event it does not cause a great lowering of pH.

$$4.RH^{+} + 2\ Ca^{2+} + 2\ HCO2 + S04^{2-} \rightarrow .2R2Ca^{2+} + 2\ H20 + 2\ CO2\uparrow + S04^{2-} + 2\ H^{+}$$

$$4RNa^{+} + 2Ca^{2+} + 2HCO2^{-} + SO4^{2-} \rightarrow 2'R2Ca^{2+} + 4Na^{+} + 2\ HCO2^{-} + S04^{2-}$$

$$2H^{+} + 4Na^{+} + 2\ HCO2^{-} + 2S04^{2-} \rightarrow 2\ H2O + 2CO2\uparrow + 4Na^{+} + 2S04^{2-}$$

Hot lime-hot ion-exchange softening combines the older softening process whereby lime is added to water to precipitate calcium and magnesium followed by cation-exchange po1ishing of the clarified water for more complete softening:

$$2\ Ca(OH)2 + Ca(HCO), + MgCl2 \rightarrow 2\ CaCO,\downarrow + Mg(OH)2\downarrow + CaC12 + 2\ H2O$$

$$2RNa+ + CaC12 \rightarrow RaCa2+ 2\ NaC1$$

Hot-process lime softening carried out at a temperature of 212°F or slightly higher permits the treatment of large quantities of water in a relatively compact unit with high chemical efficiency. It is important that the secondary ion-exchange process be conducted at a high temperature for the conservation of heat in the system and the

minimization of capital otherwise required for beat exchangers.

Several processes are being considered for the deionization of brackish waters, a program of intensifying governmental interest. Most prominent are the Kunin (Rohm .to; Haas Co.) (32), SuJ-biSul (Nalco Chemical Co.) (33), and Sirotherm (Commonwealth Scientific and Industrial Research Organization, Australia) (34) processes. Each involves the use of weak base-weak acid resin systems. Each is designed to minimize the cost of chemical regeneration. The Sirotherm process is still in the early development stage; the 'goal is to regenerate thermally, relying on the lower base strength of some anion exchangers at elevated temperatures.

Chemical Conversion.. One example is the spent phosphoric or acetic acid liquors from the pickling of aluminum and magnesium sheet. Ion exchange enables more efficient use of the acid, by substituting the lower-cost H_2SO_4 as *a* source of hydrogenions, and providing better plant control for uniform pickling operations (35,36).

$$3\ RH^+ + AlPO \rightarrow H_3PO_4 + R_2Al^{3+}$$

$$2\ R_3Al^{3+}\ 3H_2SO_4 \rightarrow 6RH^+ + Al_2(SO_4)_2$$

Chemical Purification. Purification of water-soluble nonelectrolytes such as glycerol, glycols sugar, and formaldehyde is accomplished by deionization methods analogous to those used in water treating (37,3S). Purification of synthetic amino acids such as glycine may be accomplished by absorption on a cation exchanger to the exclusion of the anion

contaminants followed by ammonia elution and acid regeneration (39):

$$2RH+ + NH2CH2COOH + NH4CI \rightarrow RH.NH2CH2COOH + NH4 + + HCI\ R$$

$$RH.NH2CH2COOH + NH3 \rightarrow RNH4 + NH2CH2COOH$$

$$RNH4+ + HCI \rightarrow RH+ + NH4CI$$

Iron removal in the purification of hydrochloric acid may be accomplished by the use of an anion-exchange resin which extracts the negatively charged iron chloride complex (40). Regeneration is accomplished 'with water at a pH sufficiently low to prevent hydrolysis.

$$RCI^- + FeCI4 \rightarrow RFeCI4^- + CI^-$$

$$RFeCI4^- \xrightarrow[H+]{H2O} RCI^- + FeCI3$$

Chemical Concentration. Metals may be concentrated in solution by extraction at a low concentration level and stripping (regenerating) at a high concentration. Thus in the case of magnesium from seawater,

$$MgCI2\ (dilute) + 2\ RNa+ \rightarrow R2Mg + NaCi\ (dilute)$$

$$NaCi\ (coned) + R2Mg \rightarrow 2\ RNa + + MgCi3\ (coned)$$

Ion Retardation. An unusual ion-exchange phenomenon involves the use of amphoteric ion-exchange resins containing both anion and cation groups molecularly intertwined. These 'snake cage" resins were discussed under Structure and syntheses. With these resins it is possible to obtain, via column operations, a separation of an elecelectrolyte has sufficient tendency to form salt pairs with the resin (is preferentially sorbed), to retard its passage through a resin column, and to permit prior elution of the nonelectrolytes:

$$RCH2N + (CH2)3\ OOCR + = NaCI$$
$$RCH2N+(CHc)2CI^{-} + NaOOCR'$$

The process of ion retardation is particularly promising for the deionization of hmw solutes.

Similarly operated, these resins may be used for separations of electrolytes from one another and for ion metatheses. Because of the enhanced selectivity of the resin for chloride ion over hydroxide ion for example, a separation of sodium chloride from sodium hydroxide, as shown in Figure 11, is possible with water elution, but not possible with conventional ion-exchange materials. With Retardion 11A8 operated under optimum conditions of flow rate, temperature, and feed composition, a sodium hydroxide product free of chloride is obtainable with only the slightest product dilution. Sodium hydroxide appears first in the effluent, followed by sodium chloride.

If magnesium chloride and sodium bromide are dissolved in water, loaded on the ion-retardation resin, and eluted with water, two separate effluent peaks will appear, the first containing sodium

chloride, the second magnesium bromide. This example of metathesis illustrates the selectivity of the cation-resin portion for magnesium ion in preference to sodium, and of the anion-resin portion for bromide over chloride.

Acid Retardation. Conventional strong-base anion exchangers have the property of sorbing strong mineral acids from solution by a non exchange process. By operations analogous to ion retardation, salts or water-soluble nonionic species may be separated from strong acids by water elution (42).

Chelation. Chelation is defined as the equilibrium reaction between a metal ion and a complexing agent, characterized by the formation of more than one bond between the metal and a molecule of the complexing agent, and resulting in the formation of a ring structure incorporation the metal ion. Chelating resins contain a complexing

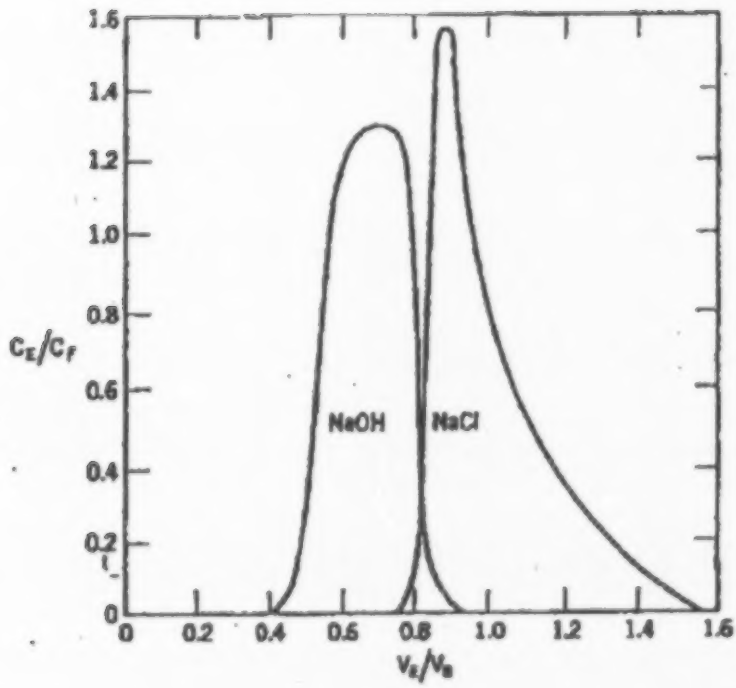

Fig. 11. Ion retardation. Chloride removal from caustic soda. Legend: Feed, 8.5% NaOH and 15% NaC1; water rinse; resin is Retardation 11A8; column size is 8 ft X 1 in. Ce/Cf = ratio of solute concentration ion effluent to that in feed. Ve?Vb = ratio of volume of effluent to bulk volume of resin bed.

group attached to the polymeric matrix. They maintain the same order of stability constants with the metal ions as their monomeric counterparts. Although many chelating structures have been incorporated in a resin matrix, they are best exemplified in commercial products by the polyamine and amino acid-type resins. An example of each has been discussed earlier under Structure and synthesis.

The formation of metal chelates with the appropriate resins makes possible the removal of these metal ions from solution even in the presence of high concentrations of noncomplexing (monvovalent) ions (16).

$$RCH_2N(CH_2COONa)_2 + Cu^{2+}\ (dil) + Na^{+}\ (coned) \rightarrow RCH_2N(CH_2COO)_2Cu + Na^{+}\ (conced)$$

Although the above reaction is rapid, the separation of a mixture of strongly boned ions, eg, the separation of Cu^{2+}, Co^{2+}, and Ni^{2+} appears to be too slow to be commercially practical.

Catalysis. By direct analogy with classical chemistry, either the functional group or the mobile ion of anion exchanger may serve as catalyst for a chemical reaction. In general, a strong-acid resin in its acid form may be substituted for hydrochloric or sulfuric acid with the added advantage of being easily filtered from the reaction mixture for reuse. Most promising large-scale applications are olefin epoxidations, hydrolysis, and esterification reactions. Some of the newer macroporous resins greatly extend catalytic possibilities, especially into nonaqueous systems such as alkylation (43). See also Molecular sieves.

Ion Exclusion. Ion exclusion is an elution process for separation ionized materials from the preferentially sorbed non or slightly ionized materials when both are present in aqueous solution (44). Because of Donnan membrane effects, ionic solutes exist at a lower concentration within the resin (gel) particles than in the surrounding solution.

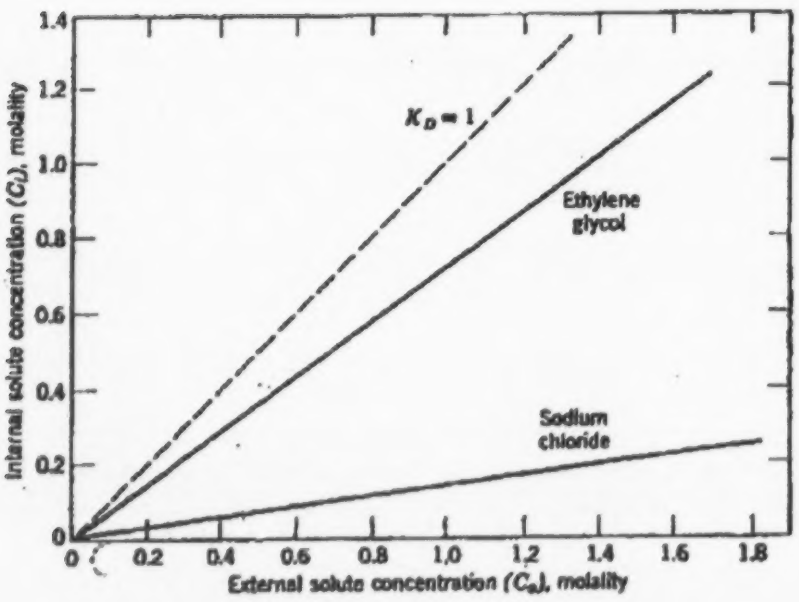

Fig. 12. Ion-exclusion principles. Distribution coefficients for ionic and nonionic solutes.

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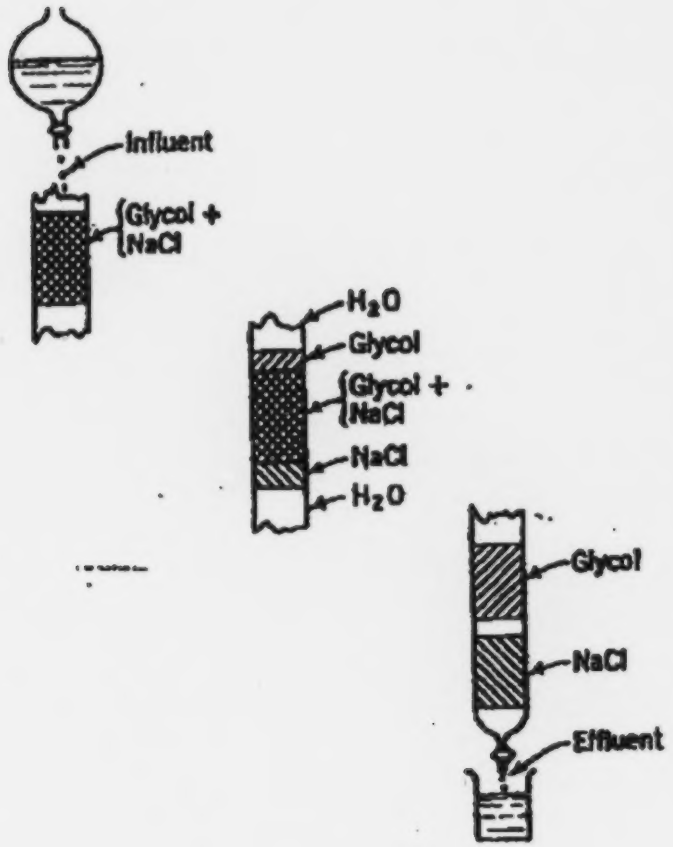

Fig. 13 Ion-exclusion separation of ionic from nonionic solutes

At the same time, nonionic solutes of lower molecular weight (<200-300_ are, as a first approximation, equally distributed between the two phases (Kd≈I). Experimental data for ionic and nonionic solutes are show in Figure 12. Thus, if a solution containing ionic and nonionic components is placed on top of a bed of resin and forced down through the column with water, the ionic material will be eluted first since it essentially has to displace only the solution in the voids (Fig. 13). The nonionic

solution must displace both the liquid in the voids and the resin liquid and will appear in the effluent after the ionic material has passed out of the column. An example is the separation of sodium chloride from ethylene glycol.

Nonionic Separations. The distribution of an organic solute between the voids liquid phase and the resin liquid phase may differ appreciably from one organic solute to another. Sugar, for example, is largely excluded from the resin liquid phase while phenol is strongly sorbed. It is thus possible to fractionate many water-soluble organic materials simply by water elution through a column of ion-exchange resign.

Phenol Removal and Concentration. Cation-exchange resigns-especially prepared from low crosslinked polymers and sulfonated to a uniform but low degree have been found to have high capacity for removal of phenol and other organic acids from solution (45). With marked increase in pH, as a caustic regeneration, the acid may be readily stripped from the column as its salt. The process would lend itself to decontamination of phenol-containing waste streams and perhaps phenol recovery.

Analytical Applications. The use of ion-exchange resigns in chemical analysis has become extremely widespread in recent years. All of the various applications previously described may be employed on an analytical basis. Many stubborn separation problems have yielded to the ion-exchange techniques. For an excellent discussion of many analytical applications see Rieman (46) and the books by Samuelson and Inezedy, (see under Bibliography, General references).

Drying. Ion-exchange materials have been found to be excellent desiccants particularly useful in the column drying of nonpolar liquids such as the hydrocarbons and halohydrocarbons (47). With modification of the supporting media they may be used in conventional drying columns. The resigns have higher water-retention capacity (10-25 lb water/100 lb dry resign) than most other drying agents, are completely insoluble, and are readily regenerated at temperatures between 250° and 300°F. See also Molecular sieves.

Plant6 Nutrition. Ion-exchanger formulations containing nitrogen, phosphorus, and potassium in addition to the minor elements that may be deficient have been found useful in fortifying a wide variety of potting soils (48). Such a fortified soil may retain a large supply of nutrient without injury to the plant. The need for frequent fertilization is eliminated; nutrition is continuous and self-regulating.

Industrial Equipment

The unique portion of industrial ion-exchange equipment is that used to house the ion-exchange material and the devices for monitoring and controlling the stream. Other components such as valving, piping, and pumps are generally conventional in chemical processing.

Ion-exchange contractors may be one of three types, viz, batch, fixed-bed column, or simicontinuous (commonly called continuous). A number of equipment firms are well qualified to design and build ion-exchange contactors for a specific end use; the use of their special knowledge is generally advisable.

Batch Reactors. Perhaps the simplest contactor. In this unit the resin is intimately mixed in a stirred vessel with the liquid to be treated for removal of the unwanted ions. A usual requirement for this type of operation is that the reaction goes essentially to completion with little excess resin, as in a neutralization reaction.

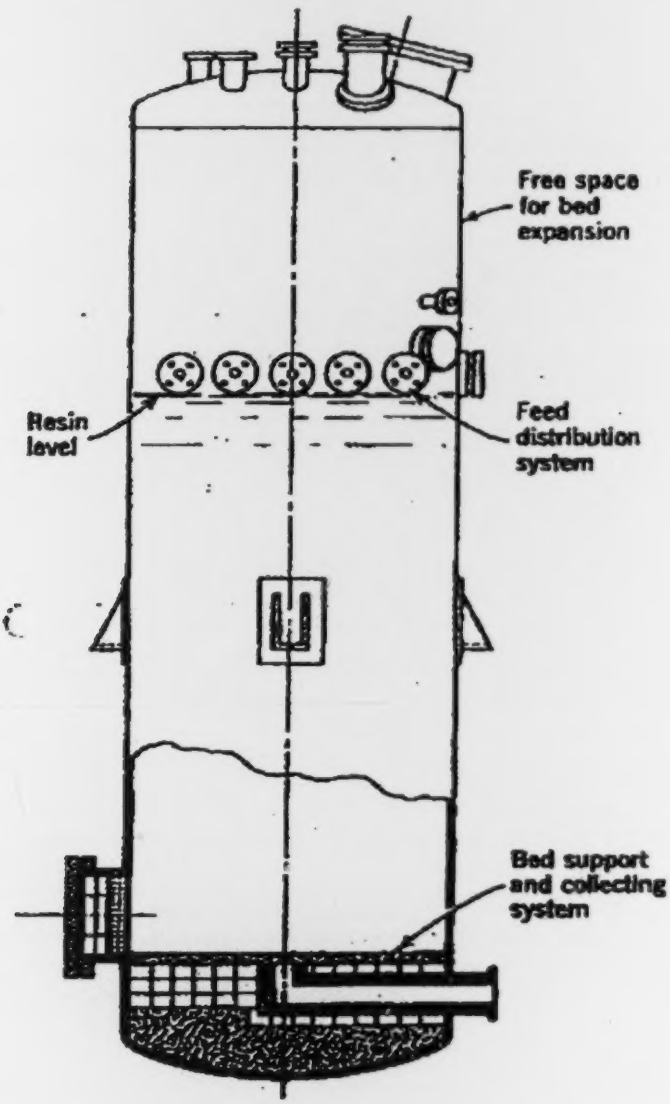

Fig. 14. Fixed-bed ion-exchange column design.

Fixed-Bed Column. The contactor type in general use is the fixed-bed column. Industrial columns range in size from a few inches in diameter to over twenty feet with multiple-column-bed heights of over 100 ft., as used in rare-earth separations.

The essential requirements for a fixed-bed column are (1) sufficient free space above the resign bed for expansion; (2) a good liquid distribution system; and (3) a good bed support and collecting system. Basic features of a typical fixed-bed column are shown in Figure 14. Operation of the fixed bed can be controlled manually or automatically. A typical control system for an ion-exchange process in which a water dome (liquid above the resin bed) is used is shown in Figure 15 (see also Instrumentation). Operations with these columns are usually sealed up directly from laboratory or mini-plant data, using 1-6 in. diam. Columns of the proposed bed depth. The fixed-bed column is expected to be the dominant ion-exchange fixture for many years.

With the expansion of uses for ion-exchange resins in the chemical processing field, many new devices or variations of the above techniques have been proposed. Some have been accepted or are in advanced development. An example of semicontinuous equipment designed to fit special conditions is the R.I.P. (resign-in-pulp) uranium

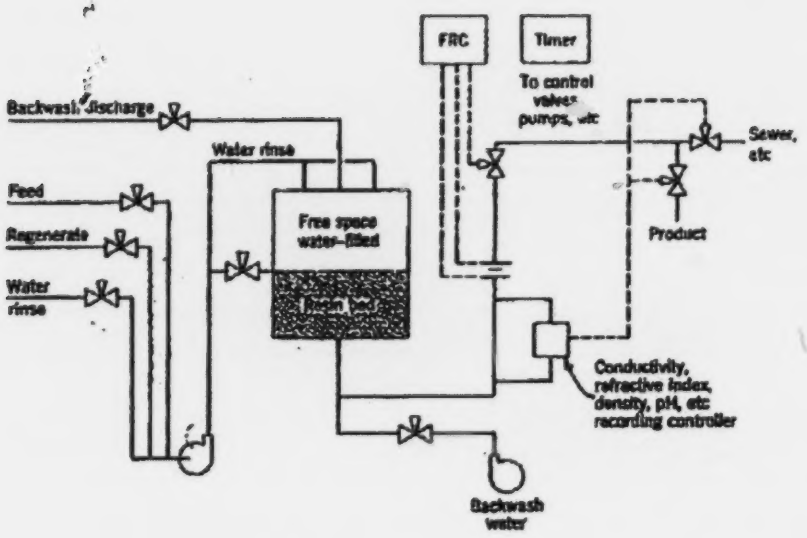

Fig. 15. Fixed-bed column control system. Hydraulic dome. FRC = flow recorder-controller.

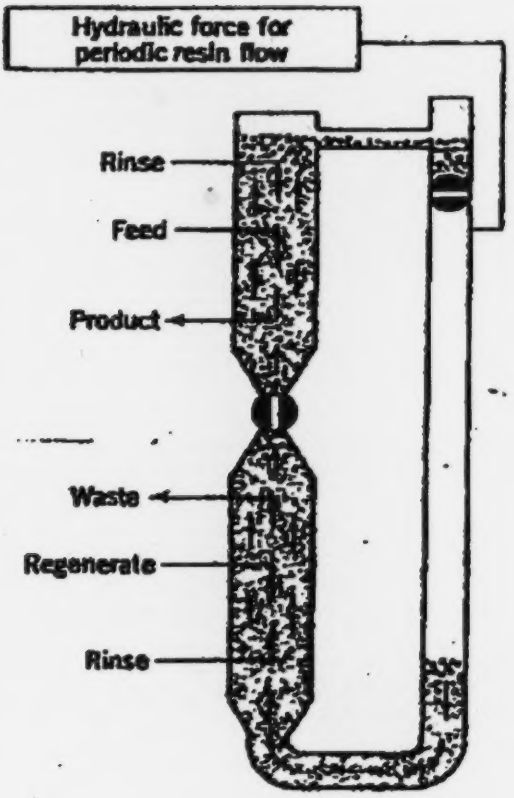

Fig. 16. Higgins contactor.
Continuous ion-exchange process.

process in which the ion-exchange material is confined to a wire basket for contact with a slurry which passes through it. Another example is the use of a stirred reactor containing a filter bed, thus combining a batch reactor for loading the resign and a fixed–bed column for elution.

United States Patent No. 6,602,502 B1

Date of Patent: August 5, 2003

METHODS AND DEVICES FOR REMOVING SPECIES

Inventor: Meir Strahilevitz, P.O Box 25008, Seattle, WA (US) 98125-1908

Notice: Subject any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

Appl. No.: 07/699,159

Filed: May 13, 1991

Related U.S. Application Data

This is a division of application Ser. No. 07/345,964, filed May 1, 1989, now U.S. Pat. No. 5,037,645, which is a division of application Ser. No. 06/925,821, filed Oct. 30, 1986, now U.S. Pat. No. 4,834,973, which is a division of application Ser. No. 06/319,238, filed Nov. 9, 1981, now U.S. Pat. No. 4,620,977, which is a continuation of application Ser. No. 05/761,290, filed Jan. 21, 1977, now U.S. Pat. No. 4,375,414, which is a continuation of application Ser. No. 05/255,154, filed May 19, 1972, abandoned.

Int. Cl.[7] A61K 39/00; A61M 37/00; C07K 1/22

U.S. Cl. 424/140.1; 210/638; 210/644; 210/645; 210/646; 210/648; 210/660; 210/661;

210/670; 530/413; 604/5.01; 604/5.04

Field of Search 604/4,5, 6, 5.01, 604/5.04; 422/70; 436/161, 824; 530/413; 210/638, 644, 645, 646, 648, 660, 661, 670, 688 424/140.1

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Primary Examiner: Saunders; David *Attorney, Agent or Firm:* Polster, Lieder, Woddruff & Lucchesi, L.C.

Primary Examiner – David Saunders
Attorney Agent, or Firm – Polster, Lieder, Woddruff & Lucchesi, L.C.

Abstract

Immunoassays of psychoactive drugs including psychotomimetic drugs, narcotic drugs, and tetrahydrocannabinols and treatment methods based on the antigenic properties of protein conjugates of these drugs. These methods are based upon treating the psychoactive substances as

haptens and utilizing their protein conjugates to produce antibodies to the psychoactive materials themselves. The immunoassay methods include both agglutination and agglutination-inhibition reactions. The treatment methods include treatment of both exogenous, administered drugs (such as cannabinols, LSD, heroin and morphine) endogenous substances (such as N,N-Dimethyltryptamine and 5-Methoxy-N,N-Dimethyltryptamine.

42 CLAIMS, 3 DRAWING SHEETS

U.S. Patent Aug. 5, 2003 Sheet 1 of 3 US 6,602,502 B1

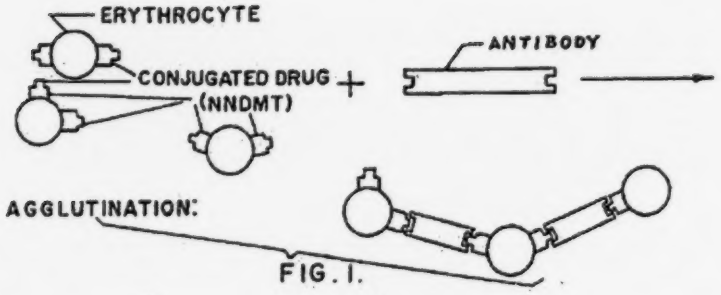


FIG. 1.

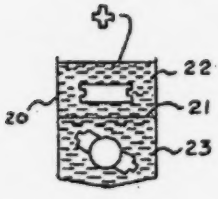


FIG. 2.

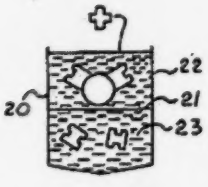


FIG. 2A

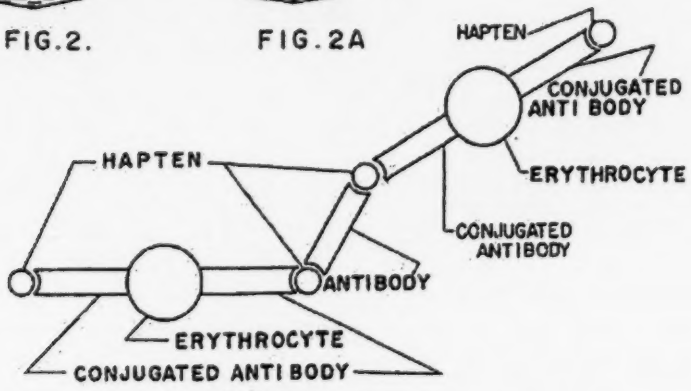


FIG. 3.

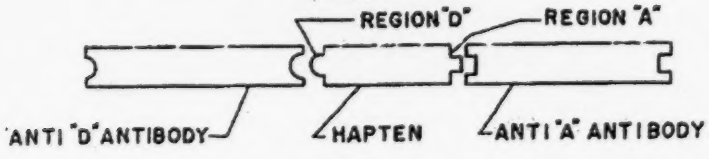
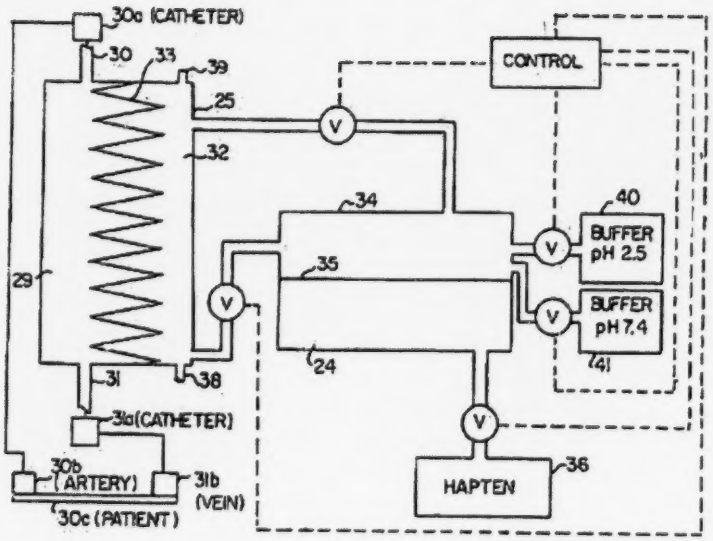


FIG. 5.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31a(CATHETER)
30b (ARTERY)
31b (VEIN)
30c (PATIENT)
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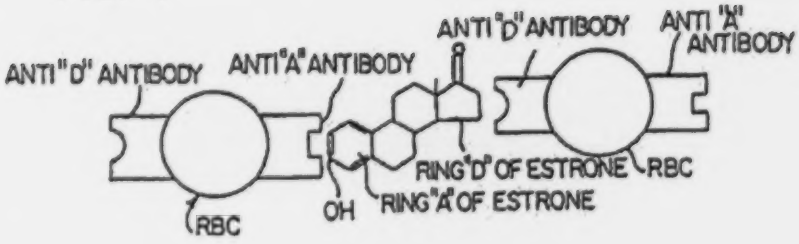
FIG. 6

FIG. 4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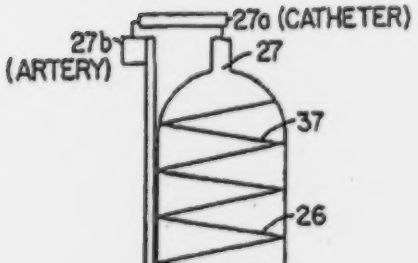
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27c (PATIENT)
28a (VEIN)
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FIG. 7

METHODS AND DEVICES FOR REMOVING SPECIES

This is a division of application Ser No. 07/3495,964 filed May 1, 1989, now U.S. Pat. No. 5,037,645, which is a division of application Ser. No. 06/925,821, filed Oct. 30, 198€ now U.S. Pat. No. 4,834,973, which is a division of application Ser. No. 06/319,238, filed Nov. 9, 1981, now U.S. Pat. No. 4,620,977, which is a continuation of application Ser. No. 05/761,290, filed Jan. 21, 1977, now U.S. Pat. No. 4,375,414, which is a continuation of application Ser. No. 05/255,154, filed May 19, 1972, abandoned.

BACKGROUND OF THE INVENTION

This invention relates to improved immunoassays of psychotomimetic drugs, narcotic drugs, tetrahydrocannabinols and other psychoactive drugs.

At the present time, there are certain methods used for the determination of psychotomimetic and narcotic drugs in biological materials.

The techniques that are used in the present time for the determination of drugs in biological materials, are described in detail in the Handbook of Analytical Toxicology (Irving Sunshine, Editor; The Chemical Rubber Company, Publisher; Cleveland, Ohio, 1969). They include in different combination for the different drugs: paper, thin layer and gas-liquid chromatographic methods, crystal tests, fluorescence, infrared, ultraviolet, thermal microscopy and animal pharmacology studies.

In general, the tests are time consuming, expensive, require expensive equipment, and require

well trained personnel. Some of the tests are not sensitive, others lack high specificity. Special difficulty is encountered in the determination of one drug in the presence of other drugs in the same biological material specimen. Thus heroin is difficult to determine in the urine in the presence of nicotine, as disclosed by D. J. Berry et al in "The Detection of Drugs of Dependence in Urine" (Bulletin on Narcotics 22, No. 3, July-September 1970; United Nations Publication). Tetrahydrocannabinols are difficult to determine in the presence of barbiturates, and complicated methods are needed for their determination in the presence of barbiturates, as described by Harold V. Street in "Identification of Drugs by a Combination of Gas-Liquid, Paper and Thin-Layer Chromatography" (Journal of Chromatography 48, 291-4, 1970).

The methods of the present invention have the advantages of simplicity, speed, specificity and low cost. They also have the advantage of being able to be applied "on the spot" (e.g. emergency room of a small field hospital). Van Vunakis et al ("Production and Specificity of Antibodies Directed towards 3,4,5-Trimethoxy-phenyl-ethylamine, and 2,5-Dimethoxy-4-methylamphetamine," Bioch. Pharmacol. 18, 393-404, 1969) were able to obtain high specificity and sensitivity in their determination, by microcomplement fixation inhibition or 3,4,5-Trimethoxy-phenylethylamine and congeners, as well as 2,5-Dimethoxy-4-Methylamphetamine and congeners. Micro-complement-fixation-inhibition is however a complicated method. Reagents have to be prepared freshly for each experiment, and they require specially trained personnel. In the methods hereinafter to be described, no such limitations are

present.

The length of time required by presently known procedures for determining psychoactive drugs also severely limits their usefulness in clinical applications.

The invention also includes immunological methods for the treatment of drug intoxication; the treatment and prevention of drug addiction, drug dependence and drug abuse; and the treatment of schizophrenia. The need for treatment methods for intoxication by psychoactive drugs, methods for freeing persons dependent on such drugs from their dependence, and methods of treating schizophrenia has long been felt. The present methods provide attractive and useful approaches to all of these needs.

SUMMARY OF THE INVENTION

In accordance with this invention, generally stated, diagnostic and treatment methods are provided by the use of the haptenic properties of psychoactive material. The term "psychoactive" includes psychotomimetic compounds containing an indol ring such as N,N-Dimethyltryptamine and its congeners and LSD 25 and its congeners; amphetamines and their congeners; narcotics such as phenanthrene alkaloids (such as morphine, heroin, codeine, hydromorphone, and levorphanol) and nonphenanthrene alkaloids (such as meperidine, methadone, and phenazocine); and tetrahydrocannabinols and other cannabinoids.

A hapten may be defined as any small molecule which by itself does not produce antibodies but which, when conjugated to a carrier protein or

other macro-molecular carrier, induces in the recipient animal or human the production of antibodies which are specific to the small molecule.

The present invention is based in part upon the application of known immunoassay techniques for haptens to certain psychoactive compounds which have not heretofore been recognized as haptens (such as N,N-dimethyltryptamine and congeners, and tetrahydrocannabinols and their congeners); in part upon the discovery of methods of adapting techniques which were heretofore used only for the determination of antibodies or complete antigens to techniques for determining haptens; in part upon the discovery of immunological treatment methods for such seemingly disparate medical problems as drug intoxication, drug dependence and schizophrenia; and in part upon the development of entirely new methods for the treatment of drug intoxication based in part upon the haptenic characteristics of the intoxicating drugs.

The discovery that 5-methoxy-N,N-dimethyltryptamine and congeners are haptens and the recognition that tetrahydrocannabinols(such as delta-9-tetrahydrocannabinol) are haptens, permits their determination by known immunoassay methods for haptens, such as radioimmunoassay (Spector et al, Science 168, page 1347, 1970; Niswender et al, in Immunological Methods in Steroid Determination, edited by Peron and Caldwell, 1970, pages 149-173) and micro-complement fixation inhibition (Levine, in Handbook of Experimental Immunology, edited by D. M. Weir, 1967, pages 707-719, especially page 712). These psychoactive haptens also may be utilized in the determination of their antibodies by methods such as

those described in Handbook of Experimental Immunology (ed. Weir), pages 423-968, for example hemagglutination (W. J. Herbert "Passive Hemagglutination" in Handbook of Experimental Immunology, pages 720-744).

The invention also encompasses the determination of haptens, and particularly psychoactive haptens, by simple and accurate agglutination and agglutination-inhibition assays.

The agglutination inhibition assay includes the steps of mixing a sample containing an unknown quantity of psychoactive hapten with a predetermined quantity of an antibody to the hapten, and then combining this mixture with a predetermined quantity of the hapten bound to an agglutinable particulate carrier. Presence of a sufficient amount of the psychoactive hapten in the sample will inhibit hemagglutination. The usual tray or other equipment may be utilized to obtain a quantitive measure of the psychoactive hapten (Handbook of Experimental Immunology, pp 782-785).

The agglutination methods involve the binding of an antibody to an agglutinable particulate carrier. This binding may require the use of a chemical binding technique such as the bis-diazotized-benzidine (BDB) technique. These techniques are set out in Handbook of Experimental Immunology, pages 737-740, Cua-Lim et al, J. Allergy 34, 142 (1963); Ingraham, Proc. Soc. Exp. Biol., N.Y. volume 99, 452 (1958).

These agglutinable carrier-bound antibodies may be used in a number of agglutination procedures. In one, a sample is mixed with the

agglutinable carrier-bound antibody in suspension, the agglutinable carrier-antibody is then mixed with a free antibody to the hapten. If the sample contains above a minimal amount of the free hapten, agglutination will result. In another method antibodies to two different sites on the hapten are prepared and bound to an agglutinable particulate carrier. Addition of a sample which contains the free hapten produces agglutination. Other procedures utilizing two different antibodies to two different sites on the hapten may be provided in which only one, or neither, of the antibodies is bound to an agglutinable particulate carrier.

In all of the agglutination and agglutination inhibition procedures, erythrocytes (red blood cells) are the presently preferred carrier. The erythrocyte may or may not be treated, for example by formalin treatment (Ingraham, supra). However, other agglutinable material such as latex or other particles may be useful in some or all of the methods.

The invention also encompasses the passive immunizationfor drug (hapten) intoxication. It is particularly directed to in vitro immunotherapy methods through immuno-dialysis or immuno-adsorbtion techniques. It also may be applied to auto-intoxication by substances etiological to diseases such as schizophrenia. For example, recent research indicates that N,N-dimethylated-indoleamines are psychotomimetic agents which are etiological to schizophrenia. See for example Tanimukai et al in Recent Advances in Biological Psychiatry, volume 10, pages 6-15 (1968); Narasimhachari et al in Biological Psychiatry volume 3, pages 21-23 (1971). Therefore, one treatment method includes the passive

immunization of schizophrenic patients with antibodies to N,N-dimethylated-indoleamines. Antibody fragments may also be used. The treatmnet of species which are etiological to schizophrenia and also are complete antigens may include the step of splitting the antibodies (for example by the method set out in Boyd, Fundamentals of Immunology (4th edition, 1966), especially at pages 70-71 in order to prevent precipitation of the species. The active immunization procedure may be used both in schizophrenia, by administration of an antigen which produces antibodies to a species which is etiological to schizophrenia (for example a protein conjugate of N,N-dimethyltryptamine), or in the treatment of drug dependent persons. The treatment includes administration of an antigen (or antigens) which produces antibodies to the drug (or drugs) on which the individual is dependent.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagrammatic representation of a hemagglutination inhibition procedure utilized in the methods of the present invention.

FIG. 2 is a diagrammatic representation of a test system of Examples 3 and 4 of the present invention.

FIG. 2A is a diagrammatic representation of a test system of Examples 5-7 of the present invention.

FIG. 3 is a diagrammatic representation of a hemagglutination reaction of the test system of Example 5 of the present invention.

FIG. 4 is a diagrammatic representation of an agglutination reaction of a test system of Example 8

of the present invention.

FIG. 5 is a diagrammatic representation of a precipitation reaction of a test system of Example 8 of the present invention.

FIG. 6 is a diagrammatic representation of an immunodialysis system of Example 12 of the present invention.

FIG. 7 is a diagrammatic representation of an immunoadsorption system of Example 13 of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples are illustrative of the methods and materials of this invention.

The following methods are utilized to produce the materials needed to carry out the invention:

a. Conjugation

The psychoactive haptens which contain an immino (NH) group (such as the N,N-dimethylated indolamines and LSD) are conjugated to Human Serum Albumin (HSA) using the Mannich formaldehyde reaction, as described by Ranadive and Sehon, Canad. J. Biochem, 45, p 1701 (1967). The conjugation in this method is to the immino (NH) group. Other hapten-macromolecular conjugates are formed by standard methods, for example those set out in Spector, in Advances in Biochemical Psychopharmacology, volume 1 (ed. Costa and Greengard) p 181 (1969); Pinckard et al in Handbook of Experimental Immunology, p 493; and Goodfriend et al in Immunologic Methods in Steroid Determination, p 15; and Ingraham, supra.

Determination of conjugation is done following

the method described in Strahilevitz et al, Biological Psychiatry 3, 227 (1971), by a spectroflourometric method.

b. Production of Antibodies to Haptens

Immunizations of rabbits with conjugates in complete Freund's Adjuvant are carried out by a similar procedure to the one described by Strahilevitz et al, supra. The preparation of antisera and globulin fractions are also described in this reference. The antibodies may be purified by known methods such as those set out in Immunologic Methods in Steroid Determination.

c. Preparation of Erythrocytes (Agglutinable Particulate Carrier)

Preparation of formalinized, type O human erythrocytes is done according to the methods described by Ingraham, supra. Some cells prepared by this method can be used even 15 months after preparation.

d. Binding of Haptens to Erythrocytes

Conjugation of haptens to the formalinized erythrocytes is done by the Bis-Diazotized-Benzidine technique (BDB technique).

Determination of presence of antibodies in the rabbit serum and determination of their specificity and cross reactivity in the serum of the drug-HSA-conjugate immunized rabbits is done by hemagglutination of the drug bound erythrocytes by their specific antisera and by specific inhibition of the hemagglutination in the presence Of the free drug (hapten inhibition in the presence of the free drug) (see Fultrope et al, Brit. Med. J., Apr. 20, 1963, pp 1049-54). The hemagglutination procedure is shown diagrammatically in FIG. 1. For example, inhibition of hemagglutination by NNDMT but not

by other drugs will indicate presence of antibody specific to NNDMT. Determination of presence of specific antibodies is also done by double diffusion and double diffusion inhibition studies (i.e. inhibition of the precipitation in the presence of the free drug as described by Ranadive and Sehon, supra, for Serotonin).

EXAMPLE 1

Radioimmunoassay of Tetrahydrocannabinols.

A tetrahydrocannabinol is conjugated to a protein by one of the standard methods utilized to bind steroids to proteins (Immunologic Methods in Steroid Determination). The conjugate is prepared in such a way as to produce a ratio of tetrahydrocannabinol to carrier molecule of from 4:1 to 30:1. The conjugate is emulsified in a phosphate buffer saline (pH 7.4). Rabbits, sheep or other suitable animals are immunized with from about 1/2-2 mg of the conjugate per kilogram body weight (in concentration of about 5 mg/ml PBS) in equal volume mixture with complete Freund's adjuvant. The mixture is again emulsified before injection into multiple sites, e.g. intradermally, into the foot pad, subcutaneously, and intraperitoneally. injections are made once every two weeks and blood taken from the animal, allowed to clot, and tested for antibodies, as set out in Ranadive and Sehon, supra.

Radioactively labeled (.sup.3 H) tetrahydrocannabinol (obtained from National Institute of Mental Health) in a predetermined amount, is added to the antibody to the tetrahydrocannabinol. Ammonium sulfate (or another precipitating reagent) is then added in order to precipitate the tetrahydrocannabinol-bound

antibody. The precipitate is sedimented by centrifugation and washed. The precipitate is then dissolved with a suitable solubilizing reagent (such as Tween 80 or NCS solubilizer [Amersham/Searle]). A standard curve is prepared by adding to the test solution varying amounts of unlabeled tetrahydrocannabinol to the predetermined amount of labeled tetrahydrocannabinol. The quantity of tetrahydrocannabinol in a sample is then determined by addition of the sample (e.g. serum) together with the predetermined quantity of labeled tetrahydrocannabinol and antibody. Comparison of the radioactivity count of the precipitate with the standard curve yields the amount of tetrahydrocannabinol in the sample.

EXAMPLE 2

Radioimmunoassay of 5-methoxy-N,N - dimethyltryptamine

Antibodies to 5-methoxy-N,N-dimethyltryptamine (5-MeO-N-DMT) are prepared according to the method of Strahilevitz et al, supra. 5-MeO-N-DMT is conjugated to a radioactive (.sup.131 I) protein. Radioimmunoassays are carried out using the radioactive hapten-protein conjugate, in the same manner as in EXAMPLE 1.

In EXAMPLES 1 and 2 radioimmunoassay can be modified by using the "double antibody procedure" as described by Niswender et al in Immunological Methods in Steroids Determination, p149. In EXAMPLE 1, non-labeled tetrahydrocannabinol may be conjugated to .sup.131 I-rabbit serum albumin, or to another radioactive labeled protein carrier for the purpose of being used in the radioimmunoassay procedure instead of the

radioactive .sup.3 H tetrahydrocannabinol.

EXAMPLE 3

Detection of a Specific Psychoactive Drug by a Qualitative Test

By titration, a suitable amount of antiserum specific to a drug and red cells to which this drug is conjugated, is determined. As shown in FIG. 2, tubes 20 made of plastic with a thin plastic divider 21 are used for this test system. If the drug in question is present in the sample that is being examined, as a free hapten, it will combine to the antibodies against it after the sample is introduced into the upper compartment of the tube and incubated for 15 minutes at 37.degree. c. When, after incubation as described above, the thin plastic barrier 21 in the middle of the tube 20, is broken by the needle with which the sample was put into the upper compartment 22, and the mixture of serum sample tested and the drug specific antiserum is allowed to mix with the drug-conjugated erythrocytes in the lower compartment of the tube, the presence of at least a particular quantity of the drug (or a particular range of quantities) will inhibit or prevent agglutination of the drug-conjugated erythrocytes. Thus agglutination inhibition will be an indication of the presence of free drug in the sample tested. (If the drug is carried in the serum, on a macromolecule like protein, or another macromolecular carrier, then it will be a complete antigen and precipitation may occur while the drug is incubating in the upper compartment 22 of the tube with the specific antiserum. However, hemagglutination inhibition should in addition be demonstrated in the lower compartment 23 of the tube.)

EXAMPLE 4

Quantitive Determination of Drugs.

This is done with a traysimilar to the one that is used routinely for microhemagglutination studies (see Tyrell, supra).

Serial dilutions of the tested serum is added to the upper compartment by a small syringe. The difference between the tray used for this test and the one that is being used routinely, is that the tray with the cylinders will be higher, and that each cylinder has an upper and a lower compartment divided by a thin plastic divider (as shown schematically in FIG. 2). The procedure is otherwise identical with the one previously described in EXAMPLE 3. The drug "titer" is the highest dilution in which hemagglutination will be inhibited.

Quantitive determination may also be done by the use of routinely used trays and loops used for micro-hemagglutination and microhemagglutination inhibition.

This method can be used for the determination of a wide variety of psychoactive haptens, including the N,N-dimethylated indolamines, LSD, narcotics (like heroin or morphine) and tetrahydrocannabinols, and may in principle be applied to determining any haptenic chemical or normal or pathological haptenic body metabolite.

In the above described quantitive methods, with each unknown serum sample that will be tested for the presence of drugs, a known control negative sample, and a known positive sample, that will include a known amount of drug, will be done simultaneously.

EXAMPLE 5

Qualitative Determination of Drug-Hapten by Reversed BDB Technique

Presence of Drug-Hapten in this system will be detected by hemagglutination.

As shown in FIG. 2A, tubes 20 are the same as for EXAMPLE 3. Antibody to the drug-hapten is prepared in an identical way as described in EXAMPLES 3 and 4. The anti drug-hapten antibodies are conjugated to the formalinized erythrocytes as described by Cua-Lim et al, supra, in the Reversed BDB technique. They are then placed in the upper compartment 22 of the tube. Free antibodies to the drug-hapten are included in the lower compartment 23 of the tube 20. The material tested for free drug-hapten is then injected into the upper compartment 22 and incubated. If free drug-hapten is present it will be bound to the anti-drug-hapten-antibodies which are conjugated to the erythrocytes. After the incubation, the tube is centrifuged and the red cells in the upper compartment are washed with Phosphate Buffer Saline PH 7.4 (PBS). The thin plastic divider 21 is then pierced by the needle and the material drops into the lower compartment 23. If drug-hapten is present attached to the anti-drug-hapten-antibodies that are conjugated to the erythrocytes, then hemagglutination appears indicating presence of free drug in the sample.

This is shown schematically in FIG. 3.

The method has the advantage of indicating the presence of hapten by hemagglutination rather than by hemagglutination-inhibition.

EXAMPLE 6

Quantitative Determination of Drug-Hapten by Reversed BDB Technique

The same technique described in EXAMPLE 5, is utilized for quantitative determination of drug-hapten, utilizing the tray and the other methods as described in EXAMPLE 4. Here again the presence of free drug-hapten is indicated by hemagglutination.

Addition of material containing free hapten to the upper compartment 22 and then incubated causes the hapten-drug to bind to the formalinized erythrocyte bound antibody, and in the presence of unbound anti drug-hapten antibody, agglutination will take place in the lower compartment 23.

The foregoing methods (EXAMPLES 3-6) can be adapted for use in non-animal materials such as plant materials and drug samples, as can the following two EXAMPLES.

EXAMPLE 7

Qualitative Determination for the Presence of One Drug Out of a Group of Drugs

This method utilizes a test system similar to the test system described in EXAMPLE 5. The system is identical with the exception that in the upper compartment 22, a mixture of several batches of formalinized erythrocytes is present, each batch being conjugated with an antibody to a different drug-hapten.

Similarly the lower compartment 23 contains a mixture of unbound antibodies, identical with those present in the upper compartment 22. If the antibodies, present in a free form in the lower compartment 23 and conjugated to the erythrocytes

in the upper compartment 22, are specific against drugs: A, B, C, D, E . . . and if any one of these drugs or some of these drugs is present in the tested sample, a positive reaction, indicated by a hemagglutination, will be visible in the lower compartment 23 thus indicating that one or more of the drugs A, B, C, D, E . . . are present in the sample.

A detailed analysis for specific drugs as described above will determine the specific drug or drugs which are present in the tested sample.

EXAMPLE 8

Production and Use of Antibodies to Different Sites on a Hapten

In the foregoing EXAMPLE, in order to ensure that the hapten will have at least two combining sites to combine with the antibodies, the hapten can be conjugated to the carrier protein (or another macromolecular carrier) through two different sites in the hapten molecule. For example, with estrone, conjugation will be done to rings A and D respectively in the estrone molecule by the methods described by Goodfriend and Sehon in Immunological Methods in Steroid Determination, supra. Conjugation to two different sites in the hapten with protein, can be done in various haptens by a variety of conjugation methods. The two conjugates of the hapten (in the example the protein conjugates of Estrone through ring A and D respectively) will be used for immunization of animals (such as rabbits). (Immunization with each of the conjugates is preferably done in different rabbits.) It is expected that the immunized rabbit will produce antibodies directed towards an

antigenic site on the estrone or other hapten molecule which is sterically guided by the site on the molecule through which conjugation to the protein was done. Generally the antibody will be directed toward a site away from (complementary to) the comjugated protein. Besides using different conjugation methods, other methods by which usefully different antibodies to the same hapten may be produded include the use of antibodies to the conjugate of the hapten with two different carriers, like HSA (human serum albumin) and hemocyanin or other two different carriers. Either the same method of conjugation or different methods of conjugation can be used for conjugating the hapten to the two different carriers. Each one of the two antisera may then be specific against another antigenic site on the hapten molecule. The same result may be obtained or enhanced by actively immunizing different animal species (such as sheep and rabbits) with the hapten-protein conjugate or conjugates to produce the first and second antibodies.

The antibodies to two hapten sites may be used in a number or procedures, as follows: a. Both antibodies are conjugated to red blood cells (RBC) or other agglutinable-particulate carrier like latex and placed in suspension, as in the preceding example, in a container. As shown in FIG. 4, in the presence of free hapten in the test material (e.g., free estrone) an antigenic site on the ring A or the estrone will attach itself to the antibody produced against the protein conjugate which was conjugated with estrone through ring D. Similarly, an antigenic site on ring D of estrone will attach itself to the antibody produced against the protein conjugate which was

conjugated with estrone through ring A. Therefore, the presence of at least a certain amount (i.e. a certain range) of hapten in a sample will produce agglutination. b. As shown in FIG. 5, with the use of anti A and anti D antibodies in the test system estrone can be demonstrated by precipitation in fluid or solid media. Other haptens as well can be determined by precipitation in the presence of antibodies to two different antigenic sites in the hapten. c. Other procedures may use combinations of antibodies which are bound to agglutinable particles and antibodies which are not so bound. Also, more than two different antibodies may be used.

All of the foregoing hemagglutination tests can be used in the presence of developing agents such as polyvinylpyrolidone (P.V.P.) or Dextran in order to increase their sensitivity. (Handbook of Experimental Immunology, p. 995).

EXAMPLE 9

Active Immunization Treatment of Schizophrenia

Active immunization treatment of schizophrenia is carried out with a conjugate of a psychotomimetic compound (or a combination of conjugates of such compounds) such as N,N-diemthyltryptamine, 5methoxy-N,N-dimethyltryptamine, tryptamine, and other psychotomimetic haptens, the presence of which has been described in the biological materials of schizophrenic individuals. These psychotomimetic small molecules are conjugated with protein macromolecular carrier, or with polyamine acid molecules as carriers (like: polylysine or polyarginine).

Immunization of the patient is carried out

either without the use of adjuvant or with the use of an adjuvant. This will be tried in humans only after the safety of the compound, safety of the route of immunization, schedule of immunization, and the safety of the adjuvant used if any, has been extensively studied, and determined in studies in experimental animals, by suitable methodology which is available at the present time.

Treatment of schizophrenia by active immunization with complete antigens (immunogens) that may be etiological in the disease,(either protein or other complete antigens (immunogens) will include immunization with enzymes that may be etiological in schizophrenia like: indoleamine N methyl transferase, indoleamine O methyl transferase, catechol amine N methyl transferase, catechol amine O methyl transferase as well as other enzymes that may be related to the etiology of schizophrenia.

EXAMPLE 10

Treatment of Schizophrenia by a Passive Immunotherapy Method

Immunization of the patient is carried out by administering antibodies to species which are etiological to the disease. For example, in acute schizophrenia, antibodies to 5-methoxy-N,N-dimethyltryptamine may be administered.

In passive immunization treatment with antibodies against complete antigens present in schizophrenia serum, in order to avoid possible precipitation of the complete antigens by the antibodies, the anitbodies may be treated in such a way as to make them "univalent", for example by mild reduction with dilute HCl and breaking of the

antibody molecule into two identical halfs each with one combining site (William C. Boyd, Fundamentals of Immunology 4th edition, Interscience Publishers New York, London, Sidney, 1966 pp 70,71). Other methods for obtaining "univalent" non-precipitating antibody, that can yet bind the antigen and possibly neutralize it are also summarized in this reference and can be utilized.

EXAMPLE 11

Treatment of Drug Dependence by Active Immunization

The immunization of drug dependent individuals is in principle similar to the immunotherapy of schizophrenia by active immunization with protein conjugates of methylated indoleamines. The drug or drugs on which the individual is dependent are conjugated to a protein or other macromolecular carrier, for example by one of the methods discussed hereinabove. After the individual is withdrawn from the drug (for example by methadone withdrawal, for heroin), he will be immunized by administration of the conjugate, in a manner similar to that used for the active immunization treatment of schizophrenia. Many conditions require the removal of species from the blood of an individual under circumstances which make active immunization and even passive immunization treatments (as well as other treatment methods) impractical. Examples of such conditions are severe intoxication (such as with phenothiazines) and certain acute schizophrenic conditions (such as acute catatonic stupor). In Addition, methods are needed for removal, from the circulation of a patient having a malignant tumor, of

certain antibodies against tumor-specific antigens. These specific antibodies are known to be "enhancing antibodies" (which stimulate the growth of the tumor). Removal of these antibodies may be therapeutic for such patients. The removal of antibodies which may be etiological in certain allergic conditions or autoimmune diseases is expected to be therapeutic for these conditions. These antibodies include the antibodies specific to the septal region of the brain, e.g. "Taraxein", which according to findings of Heath et al (Am. J. Psychiat., 124, p 1019, (1968); Arch Gen. Psychiat., 16, p 1 (1967)) are etiological in schizophrenia. It also may be desirable to remove from the circulation of schizophrenic patients other proteins such as the alpha-2 globulin which was found by Frohman et al (Ann. N.Y. Acad. Sci., 96 p 438 (1962)) in schizophrenic patients and which may be etiological in schizophrenia. In all of these conditions, one or both of the following two EXAMPLES may provide an effective treatment. Both EXAMPLES comprise connecting in the blood circulatory system of a living mammal a species-removing device, the device comprising passage means for the blood, binding means in the device for binding the species substantially specifically, and exposure means in the device for exposing the species to the binding means and for preventing the binding means from entering the mammal's circulatory system. Preferably, the species is taken from the group consisting of haptens, antigens and antibodies, and the binding means comprises a compound taken from the group consisting of antibodies, antigens and haptens which react specifically with the species. In one embodiment, the device includes a first chamber and

a second chamber, a semipermeable membrane separating the first and second chambers, means for connecting the first chamber in the circulatory system, and closed regenerative means connected in a fluid circuit with the second chamber, the regenerative means comprising means for drawing a liquid phase from the second chamber to a third chamber in the regenerative means, means for adding a reagent to the liquid phase to release a first species (illustratively the species removed from the blood) from a second species (illustratively the binding means) in the third chamber, means for removing the first species from the third chamber and means for returning the second species to the second chamber. In another embodiment, the exposure means comprise blood passage means in the device, the blood passage means comprising a matrix, the binding means being bound to the matrix.

EXAMPLE 12

Immunodialysis Treatment Primarily for Drug Intoxication

This system is particularly well adapted for the removal of haptens from the circulatory system. All of the apparatus, compartments therein and the materials used with it are of course sterile. In brief, as shown in FIG. 6, a column 25 is divided into a first compartment 29 and a second compartment 32 by a semipermeable membrane 33. Such membranes, having various pore sizes, and thus which are permeable to molecules of various sizes are commercially available. The first compartment 29, an inlet 30 for a catheter 30a which is to be connected to an artery 30b of the patient 30c to be

detoxified or otherwise treated, and an outlet 31 connected to a catheter 31a which is to be connected to a vein 31b of the patient 30c, together comprise a blood flow passage through the column 25. The second compartment 32 includes the heterologous antibody directed against the hapten which is to be removed. The antibody is contained in an isotonic solution or other solution such as those used in conventional dialysis treatment ("artificial kidney"). If the hapten is not known, (as in a patient suffering from an overdose of an unknown psychoactive drug), the solution in the second compartment 32 may include a mixture of antibodies to drugs which may be implicated. The semipermeable membrane is folded or pleated so that the surface area of interaction between the patient's blood and the antibody to the drug in the compartment 32 will be as great as possible. The semipermeable membrane is chosen to be of such a porosity and permeability as to be permeable to small molecules like the intoxicating hapten of interest, but is not permeable to large molecules present in the blood of the patient such as serum proteins.

Because the antibodies specifically bind drug molecules that diffuse from the blood of the patient in compartment 29 to compartment 32 through the semipermeable membrane 33, a continuous gradient is present for this intoxicating drug in the patient's blood that therefore continues to diffuse from compartment 29 to compartment 32 as long as compartment 32 includes antibodies directed against the intoxicating drug which are free to bind molecules of the intoxicating drug.

The dialysis system, thus far described, has great advantages over simple blood dialysis, in that

it is more specific, and, because of the high speed of binding of free hapten by the antibody to it, the system will generally require a smaller apparatus, and the time for detoxitication will be much shorter than required by the use of simple dialysis ("artificial kidney"). The chance of saving the patient's life will therefore be increased. It may also be possible to use vein to vein catheterization of the patient rather than arterial catheterization because detoxification will be accomplished faster.

When the dialysis system thus far described has been used until the antibody is exhausted for practical use, the solution of the antibody-bound hapten may be removed through a drain 38, and fresh antibody solution is added immediately through filler opening 39. The used antibody-bound hapten may be regenerated for use by the following steps: addition of glycine phosphate buffer, pH 2.5 to separate the hapten from the antibody; repeated washings with glycine buffer, each time filtering the solution by a positive pressure system through a semipermeable membrane which is permeable to all of the solution except the antibody; addition of PBS buffer, pH 7.4 to the free antibody; and sterilization of the antibody solution by passing it through a bacterial filter, i.e. one which is permeable to the antibody but not to bacteria. The solution is then ready to be reintroduced to the chamber 32. This regeneration of the system makes it far more economical than it otherwise would be.

As shown in FIG. 6, the system may also be automatically regenerated, thereby maintaining its efficiency continuously if desired, and in any case simplifying the maintaining of the sterility of the system. In this system, the hapten-antibody is

withdrawn from the second chamber 32 and delivered to a first chamber 34 of a cleaning column. Glycine phosphate buffer pH 2.5 is added from a container 40 and differential pressure is applied to accelerate migration of the free hapten across a semipermeable membrane 35 into a second chamber 24 of the cleaning column. The hapten is drained in solution into a reservoir 36, for disposal or subsequent recovery and testing. The free antibody solution is then returned to a pH of 7.4 by the addition of phosphate buffer saline from container 41. The free antibody is then ready to be returned to the second chamber 32 of the column 25. The entire process of regenerating the antibody may be controlled automatically by known differential pressure, valving and control equipment.

EXAMPLE 13

Immunoadsorption Treatment.

This treatment system is adaptable to the removal of virtually any reactive species in the blood, but is particularly well adapted to,and described herein with reference to, the removal of haptens, complete antigens, and antibodies by immunological processes. As shown in FIG. 7, the apparatus for this method consists of a column 26 which includes a matrix 37 to which a binding species is linked. The binding species is a hapten, antigen including a hapten conjugated to a carrier)or antibody which reacts specifically with the species which is to be removed from the blood. The linkage of the binding species to the matrix 37 may preferably be directly to the matrix, as when the matrix is made of a synthetic polymer such as polystyrene-latex. The linkage may also be through a

suitable solid phase coating on the matrix. The antibody is then liked to the coating by one of the known methods for the preparation of immunoadsorbents, for example by a modification of one of the methods of Campbell (Campbell et al, Proc. Nat. Acad. Sci., U.S.A., 37, p. 575 (1951); Malley and Campbell, J. Am. Chem. Soc. 85, p. 487 (1963)). If any chance exists that the solid phase adsorbent may break loose from the matrix 37, suitable filters are necessary in the system. The matrix may simply be the wall of the (plastic) column if the length of the column is sufficient to provide the required surface area for interaction at the blood-binding species interface. Preferably, the matrix 37 provides a very large surface area. Such matrices include a spiral structure, as shown in FIG. 7, which requires the blood to travel in a thin layer over a large surface. Other matrices include a honeycomb (open porosity) matrix and a fill of plastic beads.

The upper part 27 of the column 26 is connected with tubing to a catheter 27a that is connected to an artery 27b of a patient 27c being treated and the lower end 28 of the column is connected to a vein 28a of the patient 27c being treated. The blood of the patient flows through the column and the species in the blood to which the binding species is specific becomes bound to the binding species, hence to the matrix. Therefore, the blood which flows from the column 26 is relatively free of the species sought to be removed.

When the column 26 has been removed from the patient, it may be renewed by elution of the species which is bound to the binding species, by known techniques, such as washing with glycine

phosphate buffer, pH 2.5.

Numerous variations in the materials, devices and methods of this invention, within the scope of the appended claims, will occur to those skilled in the art in light of the foregoing disclosure.

CLAIMS

Having thus described the invention, what is claimed and desired to be secured by Letters Patent is:

1. A method of removing from blood a species in said blood, comprising passing said blood through a species-removing device, said device comprising passage means for said blood, binding means in said device for binding said species substantially specifically, and exposure means in said device for exposing said species to said binding means and for preventing said binding means from leaving said device, a step of connecting a closed regenerative means in a fluid circuit with said device by means of valving, a further step of separating said species from said binding means by automatically operating said valving, and a further step of reusing said device to remove said species from blood.

2. The method of claim 1 wherein the binding means binds immunologically with the species.

3. The method of claim 1 wherein the regenerative means comprises a buffer, said step of separating said species from said binding means comprising exposing said binding means to said buffer to release said species from said binding

means.

4. The method of claim 1 wherein the regenerative means comprises a first buffer, said step of separating said species from said binding means comprising exposing said binding means to said first buffer to release said species from said binding means, and including a step, before the reuse step, of exposing said binding means to a solution including a second buffer.

5. The method of claim 1 wherein said method includes operation of said valving to separate said species from said binding means without physically removing said device from a source blood.

6. The method of claim 5 wherein said exposure means comprises a semi-permeable membrane.

7. The method of claim 5 wherein said valving is connected for drawing fluid from said device into a chamber.

8. The method of claim 7 wherein said chamber includes a semipermeable membrane, the separating step including a step of removing said species after it has passed through said membrane.

9. The method of claim 1 wherein said device is connected into the circulatory system of a living mammal, the device removing a species from the blood of the mammal.

10. The method of claim 1 wherein said species is selected from the group consisting of haptens and antigens, and wherein said binding means binds immunologically to the species.

11. The method of claim 10 wherein said binding means is a complete antibody.

12. The method of claim 1 wherein said

blood is recirculated through said device for further removal of said species.

13. A device comprising a passage; binding means in said device for binding a species substantially specifically, said binding means being in fluid communication with said passage; exposure means in said device for exposing said species to said binding means and for preventing said binding means from leaving said device; closed regeneration means for separating said species from said binding means for reuse of said binding means in said device; valving for selectively connecting said closed regeneration means in fluid communication with said binding means, and control means for automatically operating said valving.

14. The device of claim 13 wherein the closed regeneration means includes means for exposing said binding means to a reagent to release said species from said binding means.

15. The device of claim 13 wherein said closed regeneration means comprises a first container for a first reagent, and a valve selectively connecting said first container in fluid communication with said binding means to release said species from said binding means, said valve being controlled by said control means.

16. The device of claim 15 further including a species-collecting valve operated by said control means for withdrawing said separated species.

17. The device of claim 15 wherein the closed regeneration means comprises a second container for a second reagent, the second reagent being chosen to return said binding means to a regenerated condition, the control means selectively

sequentially connecting said first container and said second container in fluid communication with said binding means.

18. The device of claim 13 wherein said exposure means comprises a semi-permeable membrane.

19. The device of claim 18 wherein said valving is positioned to draw fluid into a chamber.

20. The device of claim 19 wherein said chamber includes an inlet, an outlet, a semipermeable membrane positioned between the inlet and the outlet, and a valve controlled by said control means, said valve being positioned to control flow of fluid from said chamber through said outlet.

21. A method of removing from a living mammal a species in the blood of said mammal, comprising connecting in the blood circulatory system of said mammal a species-removing device, said device comprising passage means for said blood, binding means in said device for binding said species substantially specifically, and exposure means in said device for exposing said species to said binding means and for preventing said binding means from entering said circulatory system, a step of connecting a closed regenerative means in a fluid circuit with said device to separate said species from said binding means without physically removing said device from said living mammal, and a further step of reusing said device to remove said species from the blood of said living mammal.

22. A device comprising a passage; immunological binding means in operative communication with said passage for binding a species substantially specifically; exposure means in said device for exposing said species to said binding

means and for preventing said binding means from leaving said device; and closed regenerative means for separating said species from said binding means for reuse of said binding means in said device, said regenerative means comprising a reagent, valving selectively connecting said reagent in fluid communication with said binding means to release said species from said binding means, and control means for automatically operating said valving.

23. The device of claim 22 wherein said exposure means comprises a semi-permeable membrane.

24. The device of claim 22 wherein said exposure means includes a first chamber in said passage, a second chamber, and a semipermeable membrane separating the first and second chambers, said regenerative means comprising a third chamber connected to said second chamber through said valving.

25. The device of claim 24 wherein the control means is connected to the regenerative means so as to automatically draw a liquid phase from the second chamber to said third chamber.

26. The device of claim 25 wherein the control means is connected to the regenerative means so as to automatically add the reagent to the liquid phase to release said species from said binding means.

27. The device of claim 26 wherein the regenerative means further comprises means for removing the species from the third chamber and means for returning the binding means to the second chamber.

28. The device of claim 22 wherein the reagent is a buffer.

29. A device comprising a first chamber, said first chamber having an inlet and an outlet, a second chamber, and a semipermeable membrane separating the first and second chambers, immunological binding means in said second chamber for binding a species substantially specifically; and closed regenerative means for separating said species from said binding means for reuse of said binding means in said device, said regenerative means comprising a third chamber, a reagent chosen to release said species from said binding means, valving selectively connecting said reagent in fluid communication with said third chamber, and control means for automatically operating said valving.

30. The device of claim 29 wherein the reagent is a buffer.

31. The device of claim 29 wherein the control means is connected to the regenerative means so as to automatically draw a liquid phase from the second chamber to the third chamber in the regenerative means.

32. The device of claim 31 wherein the control means is connected to the regenerative means so as to automatically add the reagent to the liquid phase to release said species from said binding means.

33. The device of claim 31 wherein the regenerative means further comprises means for removing the species from the third chamber and means for returning the binding means to the second chamber.

34. A device comprising a first chamber, said first chamber having an inlet and an outlet, a second chamber, and a first semipermeable

membrane separating the first and second chambers, immunological binding means in said second chamber for binding a species substantially specifically; and closed regenerative means for separating said species from said binding means for reuse of said binding means in said device, said regenerative means comprising a reagent, valving selectively connecting said regenerative means in fluid communication with said second chamber, and control means for automatically operating said valving, the control means being connected to the regenerative means so as to automatically draw a liquid phase from the second chamber to a third chamber in the regenerative means, so as to automatically add the reagent to the liquid phase to release said species from said binding means, and so as to remove the first species from the third chamber and return the second species to the second chamber.

35. The device of claim 34 comprising an outlet in the regenerative means and further comprising a second semipermeable membrane, the second semipermeable membrane being positioned relative to the outlet in the regenerative means to retain the binding means in the device.

36. A device comprising a passage; an immunological binding species in said device in operative communication with said passage, the immunological binding species binding a second species substantially specifically; and a closed regenerative system for separating said second species from said binding species for reuse of said binding species in said device, said regenerative system comprising a reagent container, a reagent in the container adapted to release said second species from said binding species, valving selectively

connecting said reagent container in fluid communication with said binding species bound to said second species, and a control, the control automatically operating said valving.

37. A device comprising a passage; binding means in operative communication with said passage for binding a species substantially specifically; exposure means in said device for exposing said species to said binding means and for preventing said binding means from leaving said device; and closed regenerative means for separating said species from said binding means for reuse of said binding means in said device, said regenerative means comprising a first reagent, a first valve selectively connecting said first reagent in fluid communication with said binding means to separate said species from said binding means, a second reagent, a second valve selectively connecting said second reagent in fluid communication with said binding means to return said binding means to a regenerated condition, and control means for automatically operating said valves.

38. The device of claim 37 wherein the binding means binds the species immunologically.

39. The device of claim 37 further comprising a third valve operated by said control means, the third valve removing said species from said regenerative means.

40. A closed regeneration device for separating a molecule bound substantially specifically to a binding species for reuse of said binding species, said regeneration device comprising a first reagent, a first valve selectively connecting said first reagent in fluid communication with said molecule bound to the binding species to separate

said molecule from said binding species, a second reagent, a second valve selectively connecting said second reagent in fluid communication with said binding species to return said binding species to a regenerated condition, and control means for automatically operating said valves.

41. The device of claim 40 wherein the binding species binds the molecule immunologically.

42. The device of claim 40 further comprising a third valve operated by said control means, the third valve removing said molecule from said regeneration device.

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June 21, 1966 L. G. KITCHEN 3,257,314

PROCESS CYCLING

Filed May 14, 1962 4 Sheets-Sheet 1

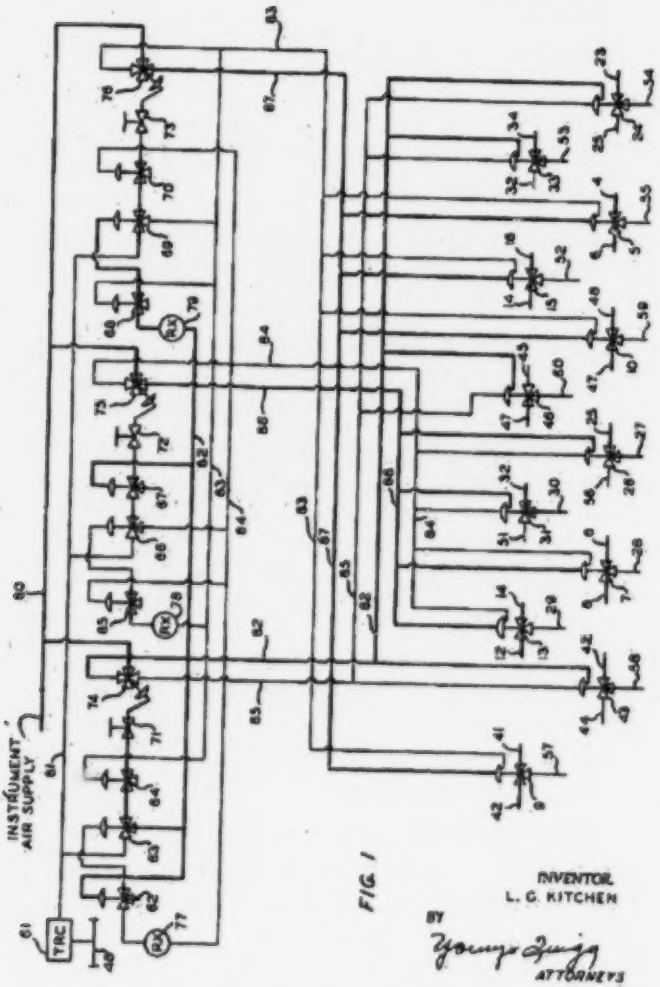

FIG. 1

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PROCESS CYCLING

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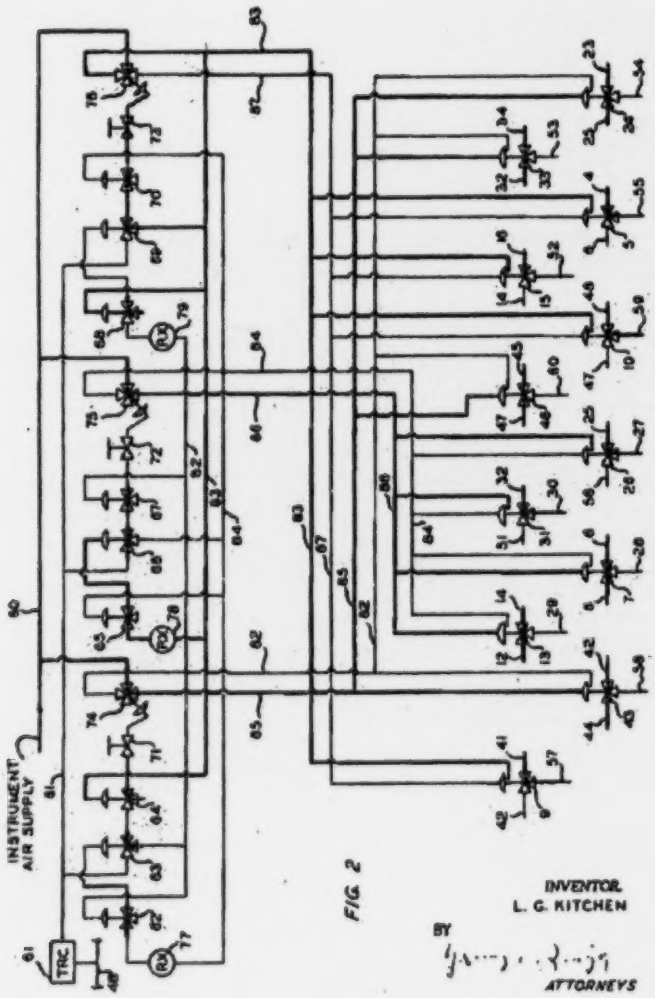

FIG. 2

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PROCESS CYCLING

Filed May 14, 1962 4 Sheets-Sheet 3

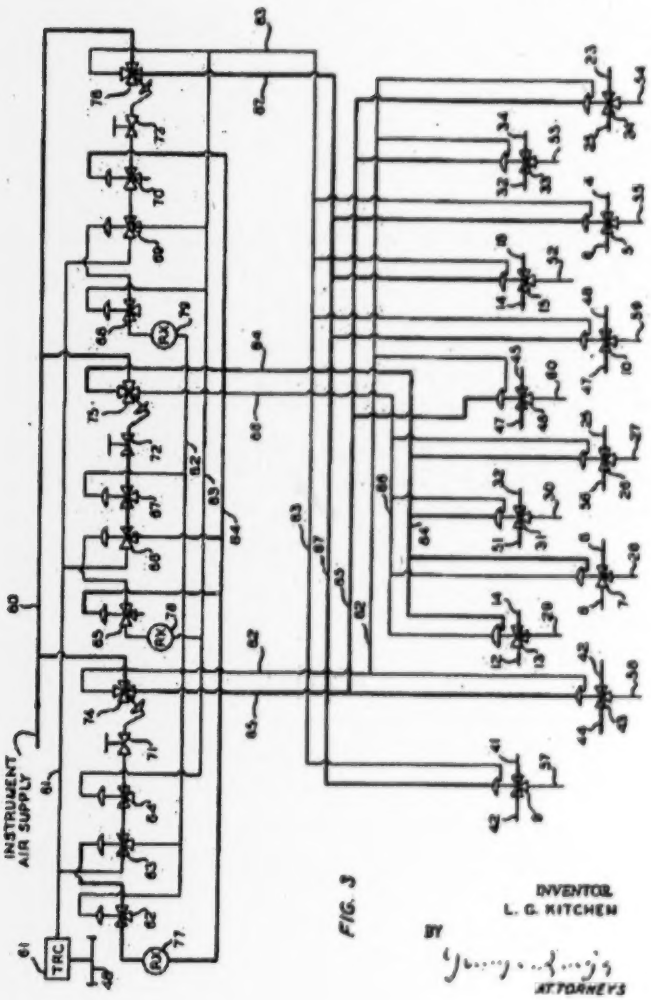

FIG. 3

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June 21, 1966 L. G. KITCHEN 3,257,314

PROCESS CYCLING

Filed May 14, 1962 4 Sheets-Sheet 4

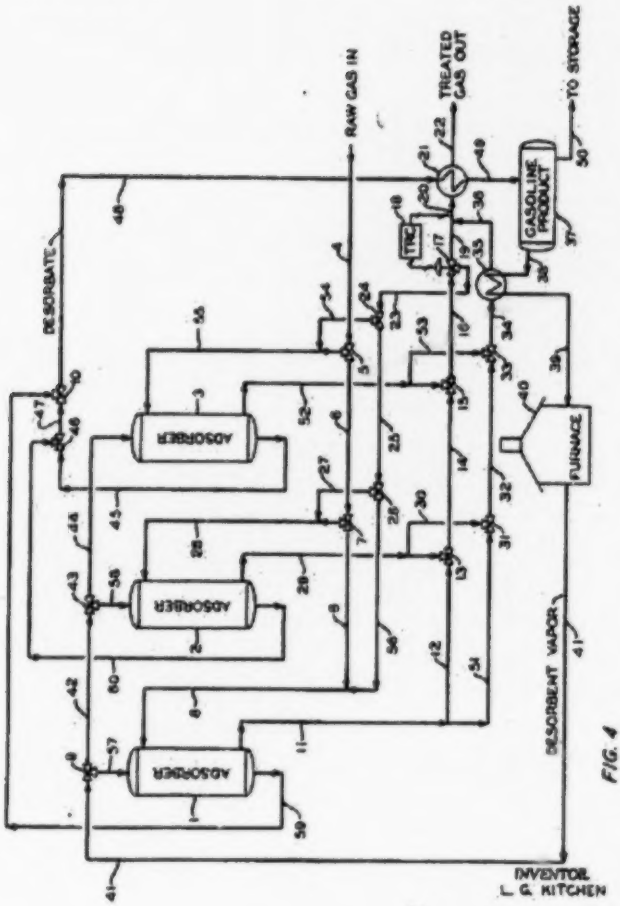

FIG. 4

3,257,314

PROCESS CYCLING

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Filed May 14, 1962, Ser. No. 194,572
6 Claims. (Cl. 210 – 30)

This invention relates to method and apparatus for cycling a process. In one of its aspects, the invention relates to method and apparatus for cycling a process through at least three-phases in response to a predetermined on-off change in the process by actuating a first group of process valves directly responsive to the change and actuating a second and a third group of process valves at a delayed time after the change such that, on the next occurrence of the change, the second group will be actuated directly responsive to the change and the other two of the groups will be actuated at a delayed time after the change and such that, on the third occurrence of the change; the third group will be actuated directly responsive to the change and the other of the groups will be actuated at a delayed time after the change. In another aspect, the invention relates to method and apparatus for switching at least three adsorbers through the cycle of adsorption, regeneration, and cooling in response to the temperature of the effluent regenerating fluid, such at each subsequent occurrence of the temperature's reaching a predetermined value effects a different one of at least three cyclic combinations of process valve group activations, the

combinations controlling which of the adsorbers is in a given phase of the cycle.

Many processes require that the same vessel or zone serve different functions during different times or phases of the process. For example, a fixed bed of catalyst; will often serve as a catalyst during one phase of a cycle and, by suitable switching of process streams, will be regenerated during another phase. During a filtration in a plate and-frame filter, cake is being built up in the apparatus during one phase of the process, the cake is washed in situ during a next phase of the process to remove occluded impurities, the cake can be removed from the apparatus by back flushing during a next phase, and the filter plates are pre-coated during a next phase. Removal of vapor from a gas by adsorption requires a step of adsorbent regeneration, usually by flowing hot gases therethrough, and then a step of cooling the regenerated adsorbent before the adsorbent is again ready to he put "on stream." These and many similar processes which are by their nature "batch" processes can be made continuous by providing a plurality of treating vessels and by switching the process streams among the vessels in cyclic manner such that one vessel is "on stream" while the other vessels are undergoing various other phases such as regeneration. In the past, such switching among vessels has been accomplished by a time-based program on the assumption that, on the average each phase will require a given time for its accomplishment. It would, of course, be economically advantageous if such switching were accomplished in response to an actual measurement of some process variable, rather than on a time basis, so that

for example the switching would automatically occur as soon as the pressure drop across a filter reached a predetermined value or as soon as an adsorbent had been properly regenerated, in order that the process stream would always have available to it the "freshest" possible vessel.

It is an object of my invention to provide method and apparatus for switching a process stream through phases of a cycle responsive to measurement of a process condition. It is another object of my invention to provide method and apparatus for switching a plurality of adsorbent beds through the cycle of adsorbing, regenerating, and cooling responsive to the effluent temperature of the regeneration fluid. It is still another object of my invention to provide method and apparatus for switching a process from one phase of its cycle to the next responsive to a measurement of a limiting variable of the process.

Other aspects, objects, and the several advantages of the present invention will become apparent upon study of this disclosure, the appended claims, and the drawing in which: FIGURES 1-3 represent three stages of operation of one embodiment of the invention, and FIGURE 4 represents application of this embodiment to cyclic adsorption process.

According to my invention, there is provided method and apparatus for regulating a cyclic process wherein a plurality of process valves are sequentially actuated to effect switching the process through phases of its cycle which comprises effecting the switching responsive to an on-off signal representative of a variable of the process. According to a presently preferred embodiment of my

invention, there is provided method and apparatus for regulating a cyclic adsorption process wherein each adsorption zone undergoes the cycle phases of adsorption, regeneration and cooling which comprises effecting the change from one phase of the cycle to the next in response to a signal produced as the temperature of the effluent fluid of the adsorption zone being regenerated reaches a predetermined value.

Referring now to the drawings for a more complete understanding of my invention, FIGURES 1-3 represent a preferred embodiment of a control system according to my invention wherein heavy lines indicate the presence of fluid under pressure; in all other aspects, these figures are identical.

A controller 61 is adapted to measure temperature (here, in conduit 48 of FIGURE 4) and to produce a continuous output signal at any time that the measured temperature exceeds a predetermined value; this signal comprises an air pressure in conduit 81. There is further provided a source of motive fluid, e.g., instrument air, in conduit 80. Three-way control valves 62-70 are pneumatically actuated such that pressure on the diaphragm motor will cause a first port to communicate with a second port, and no pressure on the diaphragm motor will cause the first port to communicate with a third port. Four-way control valves 74-76 are pneumatically actuated such that pressure on the diaphragm motor will cause a first and a second port to communicate and a third and a fourth port to communicate, and no pressure on the diaphragm will cause the first and fourth ports to communicate and the second and third ports to communicate. Hereinafter, reference to a valve port

by T, B, L, or R will refer to the top bottom, left, or right port respectively as oriented in the figure. Valves 71-73 are pressure control valves. Items 77-79 are delay relays which serve to delay an input signal for a finite time interval before reflecting a corresponding output signal. Conduits 82-87 are connected, as shown, to the control system and to the tops and bottoms of the diaphragm operators of process valves S, 7, 9, 10, 13, 15, 24, 26 and 46. These latter valves will at all times have pressure either on the top or on the bottom of their diaphragms; pressure on top connects L to R, while pressure on the bottom connects B with one of L and R. Operation of the system will now be described, with the valves being initially in the positions shown in FIGURE l and the first colum of Table I, viz., such that (referring also to FIGURE 4) adsorber 1 is on stream, 2 is being regenerated, and 3 is being cooled. In this condition, pressure from conduit 80 passes through valve 74 via ports R and T to conduit 82, holding valves 24, 33, 43 and 46 in positions R-B, R-B, R-B and L-B respectively. Pressure from conduit 80 also passes through valve 75 via ports R and B to conduit 86, holding valves 7, 13 26 and 31 in positions R-L, R-L, R-B and RB respectively. Pressure from conduit 80 also passes through valve 76 via ports R and B to conduit 87, holding valves 5, 9, 10 and 15 in positions R-L, R-L, R-L and R-L respectively. As regeneration of adsorber 2 proceeds, the temperature of the effluent regeneration fluid in conduit 48 increases until it reaches the value preset in controller 61. At this time, controller 61 sends a first pressure signal through conduit 81. This signal is blocked at valves 63 and 66, but passes through ports L and R of valve 69, ports L and R of valve 70,

and through pressure controller 73 to the diaphragm. motor of valve 76. This causes valve 76 to switch so as to connect ports T-R and L-B. Accordingly, pressure from conduit 80 is now passed via ports R and T of valve 76 to conduit 83, conduit 87 being vented via ports B and L of valve 76, causing valves 5, 9, 10 and 15 to switch to positions R-B, R-B, R-B and R-B respectively. Pressure in conduit 83 also passes to the diaphragm motor of valve 64, causing it to switch so as to connect its ports R and B and consequently venting the pressure on the motor of valve 74 via pressure regulator 71. This venting of pressure on the motor of valve 74 causes it to switch so as to connect its ports R-B and T-L; this switching then passes pressure from conduit 80 via ports R and B of valve 74 to conduit 85, and vents conduit 82 via ports T and L of valve 74. Venting conduit 82 switches valve 62 to connect ports R and L, switches valve 67 to connect ports R and L, and slowly begins to switch valve 69 via ports R and L of valve 68 and delay relay 79. This change in conditions in conduits 82 and 85 effects switching of process valves 24, 33, 43 and 46 so as to connect their ports R-L, R-L, R-L and R-L respectively. Pressure in conduit 83 (caused by switching valve 76) is also made immediately available to the motor of valve 68 causing it to connect its ports R and B, thus immediately venting the motor of valve 69 which was previously described as having begun slowly via delay relay 79. Venting the motor of valve 69 causes it to switch so as to connect its ports B and R, thus immediately applying pressure from conduit 83 via ports B and R of valve 69, ports L and R of valve 70, and regulator 73 to the motor of valve 76; loss of signal from conduit 81 will now not affect

valve 76, since it is now "locked in." It is noted that valve 75 and consequently process valves 7, 13, 26 and 31 are not affected by this sequence of events, but that pressure in conduit 83 and venting of conduit 82 switch valves 66 and 67 respectively to connect their ports L and R such that the next occurrence of a signal in conduit 81 will operate valve 75. The pressuring of conduit 83 switches valve 66 slowly because of delay relay 78; this allows dissipation of the first signal from conduit 81 so that this first signal will not operate valve 75, but the next signal will. This sequence of events just described as occurring on receiving the first signal from controller 61 will be seen to have resulted in switching the process from the initial condition of Table I, and FIGURE 1, to the middle column of Table I, or FIGURE 2, such that adsorber 1 is now being regenerated, adsorber 2 is being cooled, and adsorber 3 is on stream; moreover, the control system has been prepared for receiving the next temperature command from controller 61 by virtue of the fact that valves 66 and 67 are now aligned to pass this next signal to the motor of valve 75, it being recalled that the first temperature command operated the motor of valve 76.

The process now being on the second phase of its cycle (FIGURE 2 and middle column of Table I), the switch to the third phase; FIGURE 3 or the right column of Table I will now be described. Upon the temperature of the regeneration fluid from adsorber 1 reaching a predetermined value, a signal is again emitted from controller 61 via conduit 81. This signal is now blocked by valves 63 and 69 but passes via valves 66 and 67 and regulator 72 to the motor of valve 75, causing this latter valve to switch so as to

connect ports T-R and L-B. Conduit 84 is thus pressured, and conduit 86 is vented which results in switching process valves 7, 13, 26 and 31 to connect their ports R-B, R-B, R-L and R-L respectively. Pressuring conduit 84 also switches valve 70 to connect its ports R-B, thus venting pressure on the motor of valve 76 and causing it to switch to R-B and T-L. This pressures conduit 87 from supply 80 and vents conduit 83, which steps switch process valves 5, 9, 10 and 15 to connect their ports R-L, R-L, R-L, and R-L respectively. Conduit 82 remains vented as in the previous phase, while conduit 83 is now vented and conduit 84 is now pressured. Thus, valves 63, 64, 65, 66, 68 and 69 are switched to connect their ports L-R, L-R, R-B, R-B, L-R and R-B respectively, the action of valve 63 being slowed by delay relay 77 so as to prevent operation of valve 74 by this second signal from controller 61. Valve 75 is locked in against loss of this second signal by now receiving its motive pressure from conduit 84 via valves 66 and 67 and regulator 72. It is noted that this second sequence did not affect the position of valve 74 and consequently process valves 24, 33, 43 and 46 but has resulted in preparing valve 74 for reception of a third temperature signal from controller 61 via conduit 81 and valves 63 and 64 and regulator 71. The process is now in its third phase, and the switch back to the initial phase (FIGURE 1 or Table I, left column) will be described.

Upon temperature of the regeneration fluid from adsorber 3 reaching a predetermined value, a third signal is emitted from controller 61 via conduit 81. This signal is now blocked by valves 66 and 69 but passes via valves 63 and 64 and regulator 71 to the motor of valve 74, causing this latter valve to

switch so as to connect ports T-R and L-B. Conduit 82 is thus pressured, and conduit 85 is vented which results in switching process valves 24, 33, 43 and 46 to positions R-B, R-B, R-B and L-B respectively (their initial positions). Pressuring conduit 82 also switches valve 67 to connect its ports R-B, thus venting pressure on the motor of valve 75 and causing it to switch to R-B and T-L. This pressures conduit 86 from supply 80 and vents conduit 84, which steps switch process valves 7, 13, 26 and 31 to connect their ports R-L, R-L, R-B and R-B respectively (their initial positions). Conduit 83 remains vented as in the previous phase, while conduit 84 is now vented and conduit 82 is now pressured. Thus, valves 62, 63, 65, 67, 69 and 70 are switched to connect their ports R-B, R-B, R-L, R-B, R-Land R-L respectively (their initial positions), the action of valve 69 being slowed by delay relay 79 so as to prevent operation of valve 76 by this third signal from controller 61. Valve 74 is locked in against loss of this third signal by now receiving its motive pressure from conduit 82 via valves 63 and 64 and regulator 71. It is noted that this third sequence did not affect the position of valve 76 and consequently process valves 5, 9, 10 and 15 but has resulted in preparing valve 76 for reception of a fourth temperature signal from controller 61 via conduit 81 and valves 69 and 70 and regulator 73. The process now being returned to its initial phase, as shown in FIGURE 1, a complete cycle of the control system has been described.

Although my invention has been described as a pneumatic system, it is obvious that a hydraulic or an electrical system is also contemplated. The hydraulic system can operate using equipment

described in conjunction with the pneumatic system. In an electrical system, valves 62-70 can be replaced by relay-operated SPDT switches with "vented" ports being grounded, regulator 71-73 can be replaced by potentiometers, valves 74-76 by relay-operated DPDT reversing switches with vented ports being grounded, delays 77-79 by capacitors, supply 80 by a reference voltage source, controller 61 by a controller producing an electrical output signal, and the diaphragm operators of the process valves 5, 7, 9, 10,13, 15, 24, 26, 31, 33, 43 and 46 by solenoid operators with suitable amplifiers.

The following table presents the position of the valves in FIGURES 1-4 during the three above described process phases of the cycle.

TABLE

Valves Connect Conduits[1]

Three-Way	1 Adsorbing 2 Regenerating 3 Cooling	1 Regenerating 2 Cooling 3 Adsorbing	1 Cooling 2 Adsorbing 3 Regenerating
62	R – B	L – R	L – R
	R – B	[2]R – B	[2]L – R
63	L – R	R – B	L – R
	L – R	L – R	R – B
64	[2]R – B	[2]L – R	R – B
	R – B	L – R	L – R
65	L – R	R – B	L – R
	[2]L – R	R – B	[2]R – B
66	L – R	L – R	R – B
67			
68			
69			
70			

Four – Way Valves	(Conduits 82, 86, 87 Pressured)	(Conduits 83, 85, 86 Pressured)	(Conduits 84, 85, 86 Pressured)
74	T – R, B – L	T – L, B – R	T – L, B – R
	T – L, B – R	T – L, B – R	T – R, B – L
75	T – L, B – R	T – R, B – L	T – L, B – R
76			
Process Valves			
5	4 – 6	4 – 55	4 – 6
7	6 – 8	6 – 8	6 – 28
9	41 – 42	41 – 57	41 – 42
10	47 – 48	48 – 59	47 – 48
	12 – 14	12 – 14	14 – 29
13	14 – 16	16 – 52	14 – 16
	23 – 54	23 – 25	23 – 25
15	25 – 27	25 – 27	25 – 56
	30 – 32	30 – 32	32 – 51
24	34 – 53	32 – 34	32 – 34
	42 – 58	42 – 44	42 – 44
26	47 – 60	45 – 47	45 – 47
31			
33			
43			
46			

1 "T" is to port, "L" is left port, "R" is right port, "B" is bottom port. , Actuation delayed by one of delays 77, 78, 79.

FIGURE 4 represents the cyclic adsorption process which is controlled by the above described embodiment of my invention; this process is

disclosed and claimed in co-pending application Serial No. 172,713 filed February 12, 1962.

Although my invention has been described in conjunction with an adsorption process, it is obvious to one skilled in the art that it is not so limited, but rather is applicable to numerous cyclic processes, "batch" in nature but made continuous by employing a plurality of units in parallel, wherein it is desirable to effect switching of the units through the phases of their cycle in response to a variable of the process. Further, although the switching has been described as being responsive to temperature, it is obvious that measurement of other process variables such as pressure, flow rate, density, etc., will be advantageous depending upon the process being carried out.

Reasonable variation and modification are possible with-in. the scope of this disclosure; drawing, and appended claims to the invention, the essence of which is that there is provided method and apparatus for controlling the phases of a cyclic process which comprises effecting the switching of the process through the phases of its cycle in response to a signal representative of a process variable.

I claim:

1. The method of controlling a cyclic adsorption process wherein each of a plurality of adsorption zones under goes the phases of adsorption, regeneration, and cooling during the cycle which comprises regenerating one of said zones with a regeneration fluid, automatically effecting the switching from one to the next of said phases in response to a signal representative of the temperature of the adsorption zone being

regenerated reaching a predetermined value, and continuing said process in said now switched zones.

2. Process control apparatus for controlling an adsorption process comprising a plurality of similar adsorption processing vessels a source of fluid to be processed, a point of utility for processed fluid, conduit means communicating among said source and said point of utility and said processing vessels, a plurality of process valves in said conduit means adapted to direct the flow of process fluid from said source to various of said processing vessels and thence to said point of utility, signal generating means adapted to sense a condition of said process fluid and to produce a signal when the value of said condition equals a predetermined value, and means responsive to said signal generating means adapted to actuate said process valves step-wise through each phase of a predetermined cycle so as to control the operation of each of said processing vessels on said process fluid upon each occurrence of the producing of said signal.

3. Apparatus adapted to remove liquid from a process stream by sorption wherein said process stream is passed through one of a plurality of sorption vessels to accomplish sorption of liquid from said stream and a second of said plurality of sorption vessels is at the same time regenerated by passage therethrough of a hot regeneration fluid comprising a source of said process stream, a source of hot regeneration fluid, conduit means communicating among said sources and said plurality of sorption vessels, process valve means in said conduit means, temperature sensing means in one of said conduit means adapted to sense the temperature of the effluent from said sorption vessel which is being

regenerated and to produce a signal when the value of said temperature reaches a predetermined value, and means responsive to said temperature sensing means adapted to actuate said process valve means so as to switch the flow of said process stream and said hot regeneration fluid step-wise according to a predetermined cycle among said plurality of sorption vessels upon each producing of said signal.

4. Apparatus of claim 3 wherein there is further provided a source of cooling fluid and conduit means communicating among said sources and said plurality of sorption vessels and wherein said cycle comprises for a given of said vessels the sequence of sorption, regeneration, and cooling. .

5. Apparatus of claim 4 wherein said process stream comprises raw natural gas, said liquid comprises natural gas liquid, and said hot regeneration fluid and cooling fluid comprise respectively a vaporized portion of said natural gas liquid and a residue portion of natural gas treated by said sorption.

6. The method of controlling a cyclic adsorption process wherein each of a plurality of adsorption zones under-goes the successive phases of adsorption, regeneration and cooling during the cycle which comprises;

(a) adsorbing in a 'first of said plurality of zones a fluid to be adsorbed, simultaneously regenerating a second of said plurality of zones with a regeneration fluid, and cooling a third of said plurality of zones with a cooling fluid,

(b) measuring the temperature of the effluent from said first of said plurality of zones and automatically effecting the switching of

(1) feed from the said first of said plurality of zones to the said third of said plurality of zones,

(2) regeneration fluid from said second of said plurality of zones to said first of said plurality of zones and

(3) cooling fluid from said third of said plurality of zones to said second of said plurality of zones in response to a signal representative of the temperature of the adsorption zone being regenerated reaching a predetermined value,

(c) continuing said process in said now-switched zones until a temperature measurement of the effluent of the zone now acting as an adsorbing zone reaches the said predetermined value, and .

(d) automatically switching the said first second and third of said plurality of zones so that each is performing the function of the next preceding zone and continuing the now-switched process until a temperature measurement of the effluent from that zone which is functioning as an adsorbing zone reaches the said predetermined temperature whereupon the process will be returned to the initial condition detailed in step (a).

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